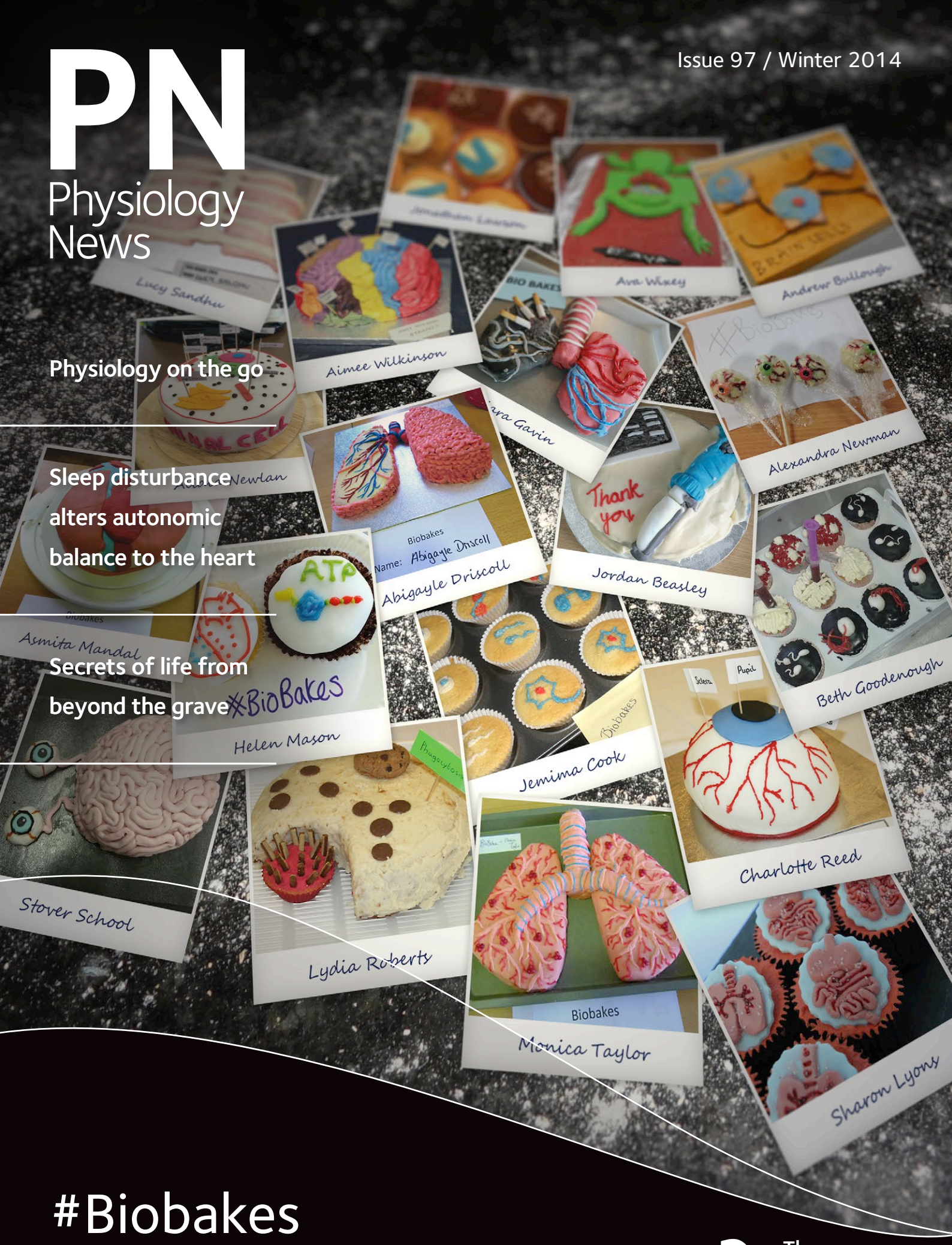
Issue 97 / Winter 2014

PN Physiology News



Physiology on the go

Sleep disturbance alters autonomic balance to the heart

Secrets of life from beyond the grave

#Biobakes

The Physiological Society

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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Undergraduate	–	£15

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2014 Biobakes entrants: Jonathan Lawson, Lucy Sandhu, Ava Wixey, Andrew Bullough, Aimee Wilkinson, Ciara Gavin, Alidia Newlan, Alexandra Newman, Abigayle Driscoll, Jordan Beasley, Asmita Mandal, Beth Goodenough, Helen Mason, Jemima Cook, Charlotte Reed, Stover School (pupils of), Lydia Roberts, Monica Taylor and Sharon Lyons.

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Deadline: 15 February 2015

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www.physoc.org/public-engagement-grants

The Physiological Society

Editorial

Mike Collis

Editor, *Physiology News*

This is my final editorial for *Physiology News* (*PN*), as I am standing down as Editor at the end of this year. When I took over as editor in 2012, I posed the question, 'Why should members pick up Physiology News to read when they have a pile of scientific papers to plough through?' I also mused about the role of a quarterly hard copy magazine in an era where information can be transmitted almost immediately through electronic media. After acting as editor of *PN* for the last three years, I am reassured that the magazine is being read widely by members of The Society (84% according to the recent membership survey). Interestingly, about 70% prefer to read the hard copy, so even in a digital age, there is still a need for a paper magazine.

A further question I have asked myself is, 'What is the unique selling point of *PN*'? Is it primarily a means by which The Society trustees and associated committees communicate with the members? Or is it a vehicle for The Society office to keep members informed of past and new ventures? Is it primarily a publication that highlights new and interesting physiological science? Or a publication that reports on members' activities – a way for The Society to promote itself to non-members? In truth *PN* is all of these, but integrating such a wide range of content from different sources needs good team work and a clear alignment of responsibility and authority. Fundamentally *PN* is (and should remain) a magazine for members, written and directed by members, with the expert help of Society staff.

I have been lucky to have had the support of a very hard working and enthusiastic editorial board. The board have a range of backgrounds, expertise and experience (including chairs of two Society committees) and broadly reflect the membership. Together we have introduced a wide range of articles: Science features and updates, the clinical application of physiological research, discussions on ethics, science policy and research funding. We have published articles on the activities of members, laboratory profiles, book reviews and, sadly, obituaries. A major innovation has been themed issues, which have featured Education, Imaging, The Pharmaceutical Industry and most recently Obesity. I am particularly proud of *PN 91*, which was produced to coincide with The Society hosting the IUPS 2013 meeting and included articles from many sister societies from around the world.

A new format and design for *PN* was introduced in 2012. The standardised format of contents has been well-received with the majority of members considering it a more enjoyable read than previously. The original re-design of the magazine received mixed comments from members and the board. We all feel that 'content is king' and that the simpler design we have now adopted provides a modern look and feel, without compromising the content or gravitas of *Physiology News*. Identifying compelling cover images for each issue, which encourage the casual reader to pick up the magazine, has been a challenge. We would welcome relevant images from members of The Society that would fulfil this important function.

This edition (*PN 97*) contains the usual diverse mix of articles. Scientific features written by members are included that present an area of research in a more 'digestible' form than is typical in a research paper or review. Feedback from members indicates that these types of accessible scientific articles are much appreciated and are often useful as teaching aids. *Physiology News* is of course not a peer- reviewed scientific journal and consequently we ensure that science based articles do not contain unpublished (un-reviewed) data. A delicate balance has to be struck between making physiological research more accessible and oversimplification. I hope that, as a board, we have got the balance right more often than not. The value of these science based articles would be increased if they could be searched easily online and I am pleased to say that there are plans to introduce a new platform for the archive to facilitate this in 2015.

There are many people who I want to thank for their support for *PN* over the last 3 years: the other members of the editorial board (Siobhan Dennis, Mike Evans, Sarah Hall, Jamie McPhee, David Miller and Keith Siew), the publications staff of The Society and of course all those who have contributed articles to the magazine. I am sure that *Physiology News* will go from strength to strength under the leadership of a new editor and wish all involved success with this important publication.

#Biobakes

As part of the activities for Physiology Friday (part of Biology Week), The Society launched its inaugural Bio-bodies baking competition. Members of the public were challenged to celebrate the human body by making a 'biological bake' and sending a picture of their 'edible cells, organs and physiological delights' to The Society via social media with the hashtag #biobakes.

With over 270 entries, the competition certainly sparked the imagination of the public. With such a large number of cakes, the top eleven entries were shortlisted before being put to a public vote. Over 4,000 votes were cast and the winner, 11-year-old Abigayle Driscoll, was announced at 5pm on Physiology Friday.

The student at Colchester County High School for Girls took the Biobakes crown with her stunning lungs cake, and will receive a £50 Amazon voucher. Runners-up included a model of the human brain, and a birthday cake in the form of a cell.

Abigayle's win was announced on Facebook and Twitter on Friday and has since been retweeted over 300 times, including a retweet from *Scientific American*. Colchester County High School for Girls also sold all their biobakes to raise funds for the Tom Bowdidge Foundation, a local young persons' cancer charity.

Many congratulations to Abigayle!

Abigayle's 'Lungs' cake took the Biobakes crown during Biology Week 2014

The Physiological Society joins the Life Science Teaching Resource Community

For several years, Society members have developed many digital teaching resources but we have not been able to find a mechanism for evaluating, managing, updating and distributing them. It became obvious very quickly that the Life Science Teaching Resource Community (LifeSciTRC) is the answer to this problem.

The LifeSciTRC is a dynamic digital repository managed by the American Physiological Society (APS) which provides teachers and lecturers with a comprehensive and diverse range of teaching aids aimed at students at different stages of their education.

Marsha Lakes Matyas, APS Director of Education Programs, says, 'We are excited to welcome The Physiological Society as the newest LifeSciTRC partner, and look forward to collaborating in other activities as well.'

Other partner organisations include the Human Anatomy and Physiology Society, the Society for Developmental Biology, the American Association of Anatomists, and the Genetics Society of America.

As a part of this community, Society members can access a range of teaching resources that can be used in their entirety or adapted to specific requirements. In essence, if you need to deliver a new teaching activity, we would strongly recommend you explore the LifeSciTRC to investigate what is already available in your subject area. This can save you time and give you new ideas for activities.

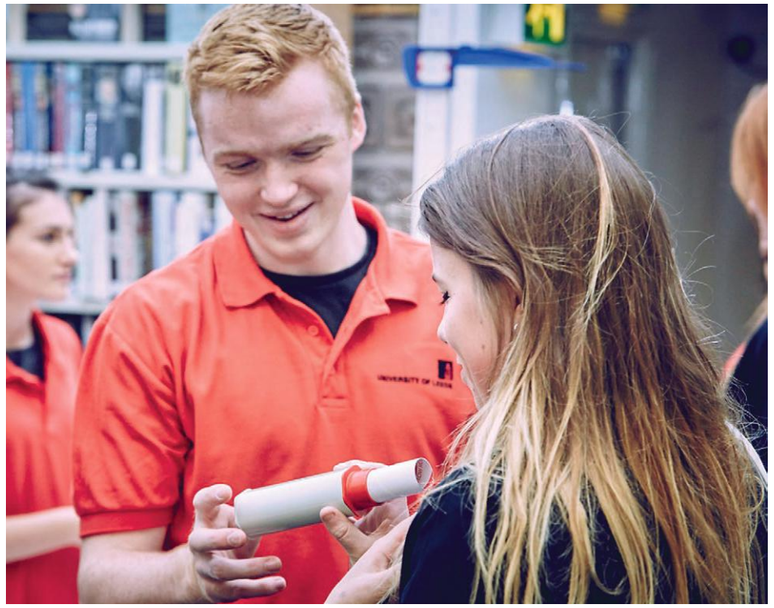
Members of the partner organisations can also submit their own teaching resources for evaluation and review by The Society - if accepted, they will be uploaded for all to use. If you have any particularly useful resources, we would encourage you to submit them so that they will benefit the whole community.

Contributions from Society members will be marked with The Society's logo, thereby establishing a community for members to use and share resources with each other. A set of FAQs for submission of teaching resources will be available via The Society's website over the next few months.

Furthermore, we are also looking for interested members to act as referees for submissions to the LifeSciTRC. If you are interested, please contact Angela Breslin at education@physoc.org

In the meantime, please take the time to register as a member of the LifeSciTRC, which is free, and explore the repository to find out which activities might be useful for your teaching, outreach or public engagement activities.

http://www.lifescitrc.org/



Student-led 'Physiology Challenge' for Biology Week at the University of Leeds

Physiology Friday, the annual event supported by The Physiological Society as a finale for 'Biology Week', aims to engage with science in a novel way. This year, the challenge was set by Dr Charlotte Haigh, an associate professor in Human Physiology at the University of Leeds, and James Croft, a final year Human Physiology student; to 'design and run a fun and engaging stall for the local Leeds public at Leeds Central Library'.

Teams of six, which each contained undergraduate BSc Human Physiology students from each year, engaged the public with a range of physiology themed stands: Alzheimer's disease and neuro-degeneration, cardio-pulmonary health, diabetes, and the science of hangovers. Rose Bavage, Outreach Officer for the Faculty of Biological Sciences, said of the event, 'It always amazes me how much undergraduates want to get involved in these activities and how much effort they put into these events. We will certainly be working with more undergraduates on public events like this in the future.'

Students evaluated the success of their efforts and were marked on the quality of their presentations, impact of their projects and the effectiveness of their engagement strategy. The activities culminated in a social quiz within the students' union bar, and marks from both the outreach project and quiz were used to select a winning team. James Croft commented, 'There is a University-wide drive to promote our research findings not only within the scientific community, but also into the public eye. The week ended in a social quiz, and, aside of anything else, outsmarting some of our lecturers was great fun!'

Chris Salmon, a third year student, elected to use peak flow meters to inform the public about obstructive disorders such as asthma, and the effects of smoking, in line with the NHS's Stoptober campaign. He said, 'It was a challenge trying to communicate principles learned in lectures to the public in a fun and easy to understand way, but we think the visitors to our stand were left feeling inspired.'

Jordan Appleyard, a second year student, designed a mountain range with the peak flow readings of famous athletes, singers, the average person and smokers to allow people to compare their peak flow readings with those of celebrities. He found the Physiology Challenge 'a great way to make friends with other Physiology and Biomedical Science students in different years, and a way to engage with members of academic staff outside lectures.'

This outreach activity was a great success and introduced undergraduate students to public engagement on behalf of both our institution and The Physiological Society. We look forward to running the Physiology Challenge again in 2015.

Physiology Feed

Bringing you snippets of the latest intriguing research

Sugar linked to memory problems and brain inflammation in adolescent rats

A diet high in sugar impaired hippocampal-dependent spatial learning and memory in adolescent but not adult rats. This research indicates that consumption of added sugars negatively affects hippocampal function, metabolic outcomes and neuroinflammation when consumed in excess during the adolescent period of development.

DOI: 10.1002/hipo.22368

Mood food – omega 3 supplements beneficial in treatment of depression

Two studies showed that omega 3 supplementation prevents detrimental chronic stress-induced emotional and neuronal impairments by impeding hypothalamic–pituitary–adrenal (HPA) axis hyperactivity, as well as depression in hepatitis C patients receiving IFN-α therapy.

DOI: 10.1038/tp.2014.77

Researchers watch dynamic motion of HIV as it readies an attack

Researchers at Weill Cornell Medical College have developed technologies that allow investigators, for the first time, to watch what they call the 'dance' of HIV proteins on the virus's surface, which may contribute to how it infects human immune cells.

DOI: 10.1126/science.1254426

Liquid DNA behind virus attacks

Researchers found that bacteriophages and herpes virus can convert their DNA from solid to fluid form, and so inject DNA into the cells of their victims. The phase transition for the studied herpes virus is temperature-dependent and takes place at 37°C.

DOI: 10.1038/nchembio.1628

How rabies 'hijacks' neurons to attack the brain

Researchers discovered that the rabies virus 'hijack' the 'train' transporting cell components along a neuron and drive it straight into the spinal cord. Once in the spinal cord, the virus catches the first available train to the brain, where it wreaks havoc before speeding through the rest of the body, shutting it down organ by organ.

DOI: 10.1371/journal.ppat.1004348

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Physiology Feed

Bringing you snippets of the latest intriguing research

Making sure antibiotics work as they should

New insight about the structure of mitoribosomes (mitochondrial ribosomes), and their different use of transfer RNA will lead the way in improving effectiveness of antibiotics.

DOI: 10.1038/nature13895
DOI: 10.1038/nature12890

Basel scientists are bringing cells on the fast track

Recent research gave novel insights into the regulating signalling pathways in time and space in order to facilitate migration of cells only in one direction. This could help to find new targets and approaches to fight cancer metastasis and inflammation.

DOI: 10.1016/j.devcel.2014.07.022

Cold exposure prompts body to convert white fat to calorie-burning beige fat

Exposure to cold temperatures can convert white fat tissue from the thighs and belly to beige fat that burns calories for heat, but this biological response is hampered in obese people.

DOI: 10.1210/jc.2014-2440

Hunger games: how the brain 'browns' fat to aid weight loss

Researchers at Yale School of Medicine have uncovered a molecular process in the brain known to control eating that transforms white fat into brown fat. This process affects how much energy we burn and how much weight we can lose.

DOI: 10.1016/j.cell.2014.09.010

Dinosaurs neither warm-blooded nor cold-blooded

Metabolic analysis suggests dinosaurs could regulate body temperature, but only to a point. Researchers compiled a database of growth rates in 381 animal species, including 21 dinosaurs and compared the speed of growth rate for each animal with energy use. They found that mammals grew ten times faster than reptiles and had metabolic rates that were ten times faster. But rather than being ectotherm, dinosaurs were found to be mesotherm (able to adjust to a metabolically favourable temperature).

DOI: 10.1126/science.1253143

Spotted some interesting research? Send it to us at **magazine@physoc.org**

Policy Focus

While politicians were enjoying summer recess, The Society's policy work was at full speed.

Engaging with Parliamentarians

Engaging Parliamentarians at H³

Following the launch of the Engaging with Parliamentarians Scheme at the House of Lords in June, we were delighted to welcome around 30 Society members to Hodgkin Huxley House in September for the Engaging with Parliamentarians training day.

The day was designed to provide information on the policy-making process, encourage members to think about policy development, and provide an opportunity to explore how policy issues are communicated by The Society. This was the first time The Society has run such an event and a number of lessons were learned. In 2015 the Policy Committee will be developing new policy positions on the key issues that were identified at the meeting as core concerns for The Society and its members. The Committee is also keen to ensure that the communication of ongoing policy work is improved, with opportunities for members to help shape policy positions.

The Health of Physiology

The Health of Physiology review is a major project being led by the President and the Chief Executive of The Society. It is reviewing physiology as a scientific, medical and educational discipline in the UK and Ireland, looking at data across a range of metrics including student numbers, research funding and publication data. In September separate stakeholder meetings were held with members and external organisations to gauge opinion.

Interestingly there was much similarity in the discussions, including – the teaching and learning of physiology in schools and universities; academic research and ties with industry; and concern for the profile of physiology and The Society. One of the recommendations for the future was for The Society to be more externally focused, with the external stakeholders encouraging greater collaboration.

The Society is currently gathering the views of industry and will also be seeking student opinion. The findings from all the key stakeholders will be incorporated into the final report and will help shape the future strategy for The Society. The report will be launched in 2015.

Letter to the Prime Minister

On 12 August The Society wrote to the Prime Minister in response to comments made by Norman Baker MP, the Home Office Minister with responsibility for animal research. He was quoted in the media as saying he wanted 'to see an end to all animal testing'. Our letter strongly urged the Government to understand the clear and vital need for the continued use of animals in research, impressing on them the need to provide clear, consistent and balanced messages on the issue.

We received a response from Mr Baker explaining that he had not called for a ban on all use of animals in scientific procedures and instead he looked forward to the day, 'in the far–off future, when science has developed techniques that make use of animals redundant'.

Section 24 reforms

In June The Society responded to a Home Office consultation on proposed changes to Section 24 of the Animals (Scientific Procedures) Act. At the time of writing The Home Office has yet to formally announce what changes will be made to Section 24; once they do we will communicate these through The Society's usual channels.

If you would like to know more about or contribute to the policy work The Physiological Society performs on behalf of its members please email Ed Hayes – **ehayes@physoc.org**

Interested in these or any other policy related issues? Please contact us via **policy@physoc.org**

Cambridge physiology scores a century – 100 years of The Physiological Laboratory, University of Cambridge

Sue Jones & Roger Keynes

Department of Physiology, Development & Neuroscience, University of Cambridge, UK

Physiology took off in Cambridge when Michael Foster arrived there in 1870. He had a remarkable influence, inspiring students and co-founding both the Physiological Society and *The Journal of Physiology*. As his Cambridge School flourished, it needed to house an increasing number of talented students and young researchers, including future Nobel laureates AV Hill (1922), FG Hopkins (1929), CS Sherrington (1932), ED Adrian (1932) and HH Dale (1936). When two disused coal cellars had been pressed into service as labs, it was clear that a new building was urgently needed. The Worshipful Company of Drapers provided funding for a fine new home, designed under the careful eye of Foster's protégé, John Newport Langley, and the Physiological Laboratory opened in full ceremony in 1914. One hundred years later, in September 2014, the Department of Physiology, Development and Neuroscience (PDN) hosted a series of events to celebrate the Centenary. Our aim was to give insight and inspiration to a wide audience about what physiology is, what it has achieved and contributed in the past, and what it continues to contribute today.

The opening event took place on 2 September 2014 with over a hundred invited guests: colleagues from across the University of Cambridge, including the Vice-Chancellor; physiologists from nearby Universities and from funding agencies, scientific journals and Societies; family members of our alumni; local Sixth Form students, and the Mayor of Cambridge. After a welcome from our Head of Department, Bill Harris, we heard from Roger Keynes about Foster's inspirational teaching and Langley's quest to understand all aspects of autonomic nervous system function, then from Andrew Murray about studies of high altitude physiology, pioneered by Sir Joseph Barcroft, continued by Sir Bryan Matthews, and still a strong area of research in the Department of PDN. Chris Huang reviewed the innovative work of past nerve and muscle physiologists, including AV Hill, Lord Adrian, Sir Alan Hodgkin and Sir Andrew Huxley. Chris also reminded us that Roger Tsien joined The Physiological Laboratory as a PhD student of Richard Adrian and then continued as a Research Fellow. Martin Johnson gave a moving account of the scientific, medical and social impact of Sir Robert Edwards's research in the field of Reproductive Physiology. Guests then visited interactive displays, where demonstrations, real experiments and a range of physiological measurements were in action. Around 40 volunteers designed and ran the displays, including graduate students, postdocs, academic staff and support staff from PDN, and there was much-appreciated help from our colleagues at Anglia Ruskin University. Sir Colin Blakemore closed the afternoon's events with a Centenary Lecture – a personal account of his experience as a young neurophysiologist in The Physiological Laboratory. Through his anecdotes and reminiscences we were reminded of further achievements in the one hundred year history of the building. Guests and volunteers then had the opportunity to mingle and 'network' at dinner in the Great Hall of Trinity College.

By all accounts the occasion was informative and enjoyable, and served as a positive reminder of the past and continuing importance of physiology. Our volunteers, in their distinctive green Centenary T-shirts, ran their interactive displays enthusiastically on three more afternoons in September for local GCSE students and interested members of the public. Further information about the Centenary events can be found at **http://www.pdn.cam.ac.uk/centenary/index.shtml**.

The events were supported by the Department of PDN, the Wellcome Trust Institutional Strategic Support Fund, The Physiological Society, Trinity College, Cambridge and St John's College, Cambridge.

Measuring action potential conduction at the Hodgkin–Huxley display

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Sir Colin Blakemore delivers the Centenary Lecture

At the Barcroft display, Sixth Form students contemplate physiology at the top of the world

Sixth Form students track the sensory-guided movements of flies using high speed cameras

Guests at the dinner in Trinity College Great Hall

All photographs courteousy of Adrian Newman

Physiology on the go

Vadim Alexeenko
University of Surrey, UK

Anna Shumitskaya
Independent telecommunications journalist

‘Physiology, as the science of body function, has always needed to record the tissue or organ response to stimuli’

Physiology is one of the health sciences that embraced the use of computers as soon as they became available, and has heavily relied on digital equipment ever since. As technology progressed, digital devices grew in capability and shrank in size and weight, ultimately becoming portable and connected, at first via wired networks. A recent boom in mobile communications has enabled portable devices to stay online and maintain the link with data processing centres virtually anytime and anywhere. This change has not yet affected the health sciences, but it is the wave of change that seems to be on its way.

Physiology, as the science of body function, has always needed to record the tissue or organ response to stimuli, and almost till the end of the last century every physiology laboratory had an extensive collection of chart recorders and paper rolls used for analogue data collection and storage. Even now, if you go through the laboratory cupboards, very likely you will find one or two such ‘fossilised’ devices. Most likely they are preserved purely for sentimental reasons, while the ‘real science’ went fully digital long ago. The major driving forces were the prospect of easy access to huge volumes of data, the power of numerical data analysis and the ability to automate the experiment.

The determination to use computers was so strong that the first electronic devices, used to control experiments or treat the patient, were bulky, consequently limiting the subject’s movements to the immediate vicinity of the apparatus (Fogt *et al.* 1978). However, the ultimate aim of life sciences is not to gather physiological data or cure a patient who is tethered by wires and tubes to a computer, but to help them have as normal a life as possible, and this means mobility.

Mobility for a medical device can come in different forms. At its simplest it takes the shape of an external device connected by sensors to a patient, like a Holter heart rate monitor or glucose monitor. More complex technologies that can augment or replace physiological functions include implantable prosthetic devices: pacemakers, defibrillators, cochlear implants, sacral neuromodulators and drug pumps. Such implants do not restrict patient movement and can substantially increase their quality of life. But these implantable digital devices overcome quite a few technological challenges. First, there is a requirement for compact and energy-efficient computers, sporting high precision analogue-to-digital and digital-to-analogue converters to interface the implant. Secondly, an appropriate set of sensors is needed to read the relevant physiological information. The list of such parameters might be long: electric potentials, blood or other liquid pressure, oxygen and glucose concentration; this list is by no means exhaustive. Thirdly, if the implantable device is intended for drug delivery, then a pump is a must. Lastly, and perhaps most importantly, an efficient and compact power source is essential to supply the implant.

Some of these tasks were solved by microfluidics technologies – tiny liquid pumps with the smallest of them being less than a few cubic millimetres. Others were addressed by development of biosensors: for example, it is now possible to detect blood glucose content using optical methods (Ozana *et al.* 2014). A highly competitive telecommunications market has helped to shrink the size of portable electronic devices, hugely increased the capacity of their batteries, and introduced wireless charging technology to the mass market. Application of the same technologies to implantable devices has brought similar benefits of decreased size and power consumption; wireless charging is now available for devices that are implanted several centimetres deep (Ho *et al.* 2014).

However, an important feature of implantable devices that has not been mentioned is that they have the ability to collect data and relay it to external data storage centres for further analysis by healthcare professionals. The increased capabilities of portable electronics make it even possible to perform a limited data analysis on the implantable or wearable device. This can restrict the uploaded data to just those segments that report deviations from the normal state and enabling the device to alert medical services and carers of potentially dangerous situations. A review analysing continuous cardiac monitoring devices, piloted in France, indicated a four-times quicker intervention response compared with conventional monitoring strategies (Maillard *et al.* 2014).

The progress of telecommunications has made the link between an implantable device and a remote data centre much more feasible than was previously possible. During the last decade, considerable effort has been directed towards the development of methods to facilitate data exchange between stationary and mobile digital devices – machine-to-machine technology (M2M). Originally conceived for automation and instrumentation, now it also covers various telematics applications, and buzzwords such as ‘connected revolution’ or ‘internet of things’ became a commonplace in the telecommunications world.

Proper functioning of such technologies requires permanent network connectivity and this might have had an influence on the paradigm shift in the design of mobile networks. The development of all previous standards of mobile communication technologies was aimed primarily at increasing the data transfer rate as the most important parameter, and loss of service in some locations was treated as a valid trade-off for high data transfer rates in the neighbouring places. The upcoming standard of fifth-generation mobile network (5G) is expected to be adopted in early the 2020s and, according to Professor Rahim Tafazolli, the head of the 5G Innovation Centre in the UK, the new standard will focus mostly on availability of digital services, with the ultimate aim of the total elimination of ‘bad reception areas’.

Other important features of 5G devices will include increased energy efficiency, reduced delays and latencies, and better management of portable device resources.

It is still too early to make any assumptions on a final shape of the 5G standard, but one can now make some informed guesses as to the possible uses of its features: mobile phones used as portable remote cardiac monitoring base stations is just one of them. The exciting possibilities for other futuristic medical gadgets may emerge very soon. And one of the key things to make it happen is a tight collaboration of telecommunication scientists and health scientists.

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A tribute to Bernhard Frankenhaeuser 1915 – 1994

Jan Lännergren
Karolinska Institutet, Sweden

‘Bernhard was one of the pioneers in computer simulation of biological processes and managed, together with Andrew Huxley, to recreate a nodal action potential using his experimental data and advanced programming’

Bernhard Frankenhaeuser was born in 1915 in the small town of Borgå in the south of Finland where his father was an architect. He went to school in Borgå and then started to study medicine in Helsinki in 1934. Late in 1939 the Soviet Union attacked Finland and the so-called Winter War started. Bernhard was called into the Finnish army and served as military doctor both in the Winter War and in the so-called Continuation War (1941–44). Very much later, he told dramatic stories about narrow escapes from the advancing enemy. When the war was over, Bernhard finished his studies and obtained his medical degree in Helsinki in 1946. In that year he also met Marianne von Wright and they married after having known each other for just a few months. Marianne later became a world authority in stress research. They had their only child, a daughter named Carola, in 1949. She is married (Lidén) and is now a Professor of Occupational and Environmental Dermatology at the Karolinska Institutet.

By 1939, Bernhard had already come into contact with Ragnar Granit, then Professor in Physiology at the University of Helsinki. After the war, Granit helped Bernhard to go to Oxford. There he met William Rushton who made a deep impression on him, as did the whole British School of Physiology. In Oxford, Bernhard undertook the experimental work that was the foundation of his doctoral thesis, which he defended in Stockholm in 1949. Bernhard had been in contact with Granit during the years after the war and moved to Stockholm (with Marianne) in 1946. Granit had already moved to Sweden in 1940 and set up a laboratory at the old Karolinska Institutet. In 1946, Granit was offered a chair at the new Karolinska and his own institute, which he accepted. Bernhard joined Granit at the new Nobel Institute for Neurophysiology in 1947.

Between 1950 and 1952, Bernhard worked on accommodation in single nerve fibres of the frog. He was also interested in the mechanism of saltatory conduction in myelinated nerve fibres. In 1952 Bernhard met Alan Hodgkin at a meeting in Cold Spring Harbor. Hodgkin and Huxley had just published their famous papers on the mechanism of nerve impulse conduction. Their voltage clamp experiments had revealed the voltage- and time-dependency of the Na^+ and K^+ conductance in the axon membrane; the ‘H-H’ equations gave a quantitative description of the mechanism underlying the nerve impulse. Still, it was not known how the opening of the ion channels in the axon membrane came about. Frankenhaeuser and Hodgkin decided to test the hypothesis that Ca^{2+} acts as a ‘plug in the hole’ that controls the conductance. This idea originated from the knowledge that the Ca^{2+} concentration of the external medium influenced excitability. Voltage clamp experiments were again performed on the squid giant axon at the Marine Biological Laboratory in Plymouth. They found that changes in Ca^{2+} concentration shifted the voltage dependency of the ion conductances – as predicted by the hypothesis – but the effect was not large enough. Nevertheless, the findings about the Ca mechanism were of great importance and this paper has been highly cited.

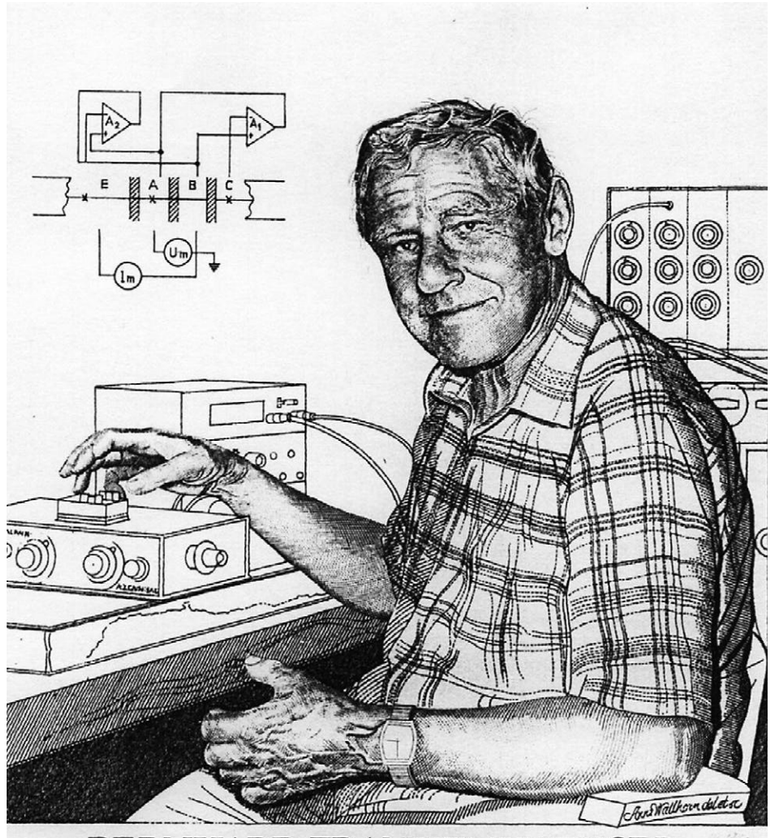
Hodgkin and Huxley had clarified the mechanism of impulse generation in squid axons. But vertebrate myelinated nerve fibres have a different structure. Huxley and Stämpfli had shown that impulse propagation in myelinated fibres is saltatory. But which ionic currents underlie the nerve impulse at the node? In order to answer this, a method was required that allowed voltage clamp of the isolated nerve fibre. After several false starts, and when Bernhard was near despair, he finally managed to get the method to work. Using negative feedback, the longitudinal currents could be controlled and the membrane potential recorded. This was decisive for allowing control of the membrane potential with yet another feed-back amplifier and obtaining a voltage-clamp system. With the new method in hand, Bernhard made a thorough analysis of the nodal ionic currents and discovered many similarities with the squid axon membrane, but also some interesting differences. Bernhard was one of the pioneers in computer simulation of biological processes and managed, together with Andrew Huxley, to recreate a nodal action potential using his experimental data and advanced programming.

One aim at the onset of the voltage-clamp experiments on the node was to try to resolve ‘quanta’ in the recorded ionic currents. The node is especially suitable for this approach because of the very restricted membrane area. Bernhard did not quite reach his goal, but his method of noise analysis was of a pioneering kind.

Bernhard had a position as researcher at the Swedish Medical Research Council between 1963 and 1965, was Professor in Physiology at the University of Umeå 1965–67, and succeeded Granit as Professor in Neurophysiology at the Karolinska Institutet and as Director of the Nobel Institute for Neurophysiology in 1967 until his retirement in 1981. A characteristic of Bernard as a scientist was his aim at perfection. He could spend many weeks, even months, at refining a technique: it was all or nothing – he would never engage in mediocre science. Bernhard is author of 49 publications listed in PubMed and contributed to at least equally as many as supervisor. For him it was natural to share his vast knowledge generously and to work with the manuscripts of pupils and colleagues.

I remember Bernhard as extremely knowledgeable about electronics: from the beginning in the laboratory he constructed his own equipment – very much the British style. He also designed a large part of the electronic equipment for other people in the department. He was very generous with his knowledge and put together a lab programme for us beginners to increase our understanding of the mysteries of electronics. Bernhard had many collaborators (post-docs) from other countries as well as a number of Swedish PhD students (including myself) of which he took very good care.

Questions about the threat to the environment were something that engaged Bernhard at an early stage. He was an ardent (and very well-informed) opponent of nuclear power and was politically active in the debate in Sweden which raged in the 1970s. He was also very concerned about phosphate eutrophication and the risk of lack of oxygen in the Baltic, as well as the use of pesticides such as DDT and PCB. Bernhard was in fact one of the pioneers in environmental science, which is now such a hot topic.



Bernhard was not only generous with his knowledge in mathematics and electronics, but also generous outside the lab. Many of us remember his summer parties at his house in Saltsjöbaden, southwest of Stockholm, close to the water, where the whole department was invited. Not far from his house, his beloved Dulcibella, a relatively big sailing boat, was moored. Some of us PhD students were recruited as crew onboard Dulcibella and sailed with Bernhard in the Åland archipelago where he tried (with mixed results) to teach us navigation and seamanship.

The starting point of this portrait of Bernhard was a photo-collage, made by some of his pupils just before his retirement. The collage was given to Arne Wallhorn, a well-known engraver and famous for his miniature engravings for postage stamps. He made a large steel engraving and, from the steel block, a limited number of prints were made. The artist has been playing a little when drawing the voltage clamp circuit and it is up to the reader to discover the error
- no prizes given!

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Dodge FA & Frankenhaeuser B (1958). Membrane currents in isolated frog nerve fibre under voltage clamp conditions. *J Physiol* **143**, 76–90.

Frankenhaeuser B (1963). A quantitative description of potassium currents in myelinated nerve fibres of Xenopus laevis. *J Physiol* **169**, 424–430.

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2015 *Forthcoming events*

28 Mar–1 Apr

Experimental Biology 2015
Boston Convention and Exhibition Center,
Boston, USA

http://experimentalbiology.org/2015/home

10–12 Apr

Ageing and Degeneration: A Physiological Perspective
Royal College of Physicians,
Edinburgh, UK

www.physoc.org/ageingtopic

6–8 July

Physiology 2015
Motorpoint Arena, Cardiff, UK

www.physiology2015.org

2016

29–31 July

Physiology 2016
The Convention Centre Dublin, Republic of Ireland

Meeting Notes

Obesity – a physiological perspective

10–12 September 2014,
St. James' Park
Newcastle upon Tyne, UK

Our first ever Topic Meeting took place at the Newcastle United Football Club, Newcastle upon Tyne. This year's theme was Obesity: a physiological perspective. With over 200 attendees, 20 symposia and 80 poster presentations, it is safe to say that the meeting was highly successful and well attended.

The conference took us on a journey into the complex nature of obesity. Topics range from causes of obesity, obesity during pregnancy and metabolic and cardiovascular consequences of obesity, to mechanisms underlying the physiology of appetite control, as well as the impact of obesity on society and possible lifestyle interventions to challenge obesity.

We are looking forward to seeing you at our next Topic Meeting, on Ageing and Degeneration, which will take place on 10–12 April 2015 in Edinburgh.

Meeting Notes

Something Old, Something New, Something Borrowed, Something... Else

4–5 September 2014,
University of Durham, UK

Guy Berwick
University of Aberdeen, UK

Rade Durbaba
Northumbria University, UK


Prof Tom Sears, Dr Guy Bewick and Dr Bob Banks

The weather was kind to the 52 delegates who gathered to recognise Dr Robert Banks's >40 year career investigating mechanical sensation. Speakers from Canada, Australia, USA, Europe and the UK jumped at the chance to participate, providing a marvellous blend of reminiscence, review, and cutting-edge sensory neuroscience in an extremely convivial atmosphere. All speakers had scientific connections with Bob, mostly as collaborators, and with the attendees made for a veritable 'Who's Who' of muscle spindle research over the last half-century. Talks ranged from higher motor control, through proprioception and into cellular aspects of mechanosensory function, encompassing humans, other mammals, invertebrates and systems biology.

The research focus throughout both days was Bob's career in muscle spindle physiology and relating this to mechanoreception as a whole, with talks from PhD students to Professors Emeritus. First day highlights included a timely reminder of how proprioceptive physiology and anatomy relate to clinical need and rehabilitation (Something Old), plus the latest research into channel distributions responsible for repetitive firing of motoneurones and muscle spindle afferents, and potential damage by chemotherapy (Something New). There was also a group photograph.

The enjoyable day was rounded off perfectly by the symposium meal of excellent Aberdeen Angus steak in the converted chapel of St Hild and St Bede - truly an atmospheric, gastronomic and social success.

For the second day, highlights included the burgeoning evidence for synaptic-like vesicles (Something Borrowed) as part of a system for autogenic regulation of stretch-evoked firing via an atypical glutamate receptor that eludes any canonical pharmacological profile, plus emerging indications that general sensory physiology principles may apply across tissues, phyla and even sensory systems (Something Else...). Every talk was followed by lively discussion, which continued into breaks around the posters displayed throughout the meeting. In this regard, an attendee of particular note was Professor Peter Matthews, the 'elder statesman' of muscle spindle physiology, who came out of retirement to attend in recognition of Bob's unique contribution to this area. His scientific enthusiasm clearly undiminished, Prof Matthews energetically and regularly contributed insightful comments and questions throughout the two days. Many old friendships were renewed and new friendships forged while celebrating Bob's extensive career as a long-time Society member and recognising the substantial advances he and colleagues have made together.

We are indebted to The Physiological Society for designating this as a Special Symposium, with associated financial support. We would also like to thank the University of Durham Biophysical Sciences Institute, Cambridge Electronic Design and World Precision Instruments for their kind sponsorship of the event. Photographs were provided by Tom Banks (Bob's photographer son).


Group photograph of attendees

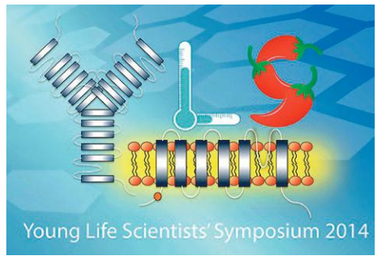
Meeting Notes

Young Life Scientists' Symposium 2014

4 October 2014,
Kings College London, UK

Aisah Aubdool

Professor Sue's Brain Lab
Kings College London, UK

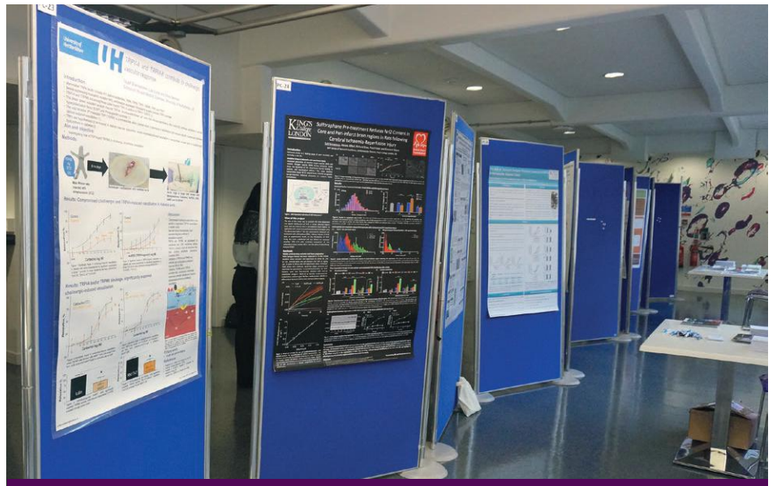


The Young Life Scientists' Symposium 2014 (YLS2014) was held at King's College London on October 2014, with the theme The Physiology & Pharmacology of TRP channels. The symposium was supported by The Physiological Society, the Biochemical Society and the British Pharmacological Society in addition to King's College London, and was sponsored by various biotechnology companies.

The symposium attracted about over a hundred national and international early-career researchers, and held vivid discussions on the cutting-edge research on the physiology, pharmacology and biochemistry of TRP channels. Additionally, YLS2014 incorporated engaging workshops on the future of publications (F1000) and outreach opportunities, including Dr Julie Keeble's experience with the Mission Discovery programme to send experiments to the International Space Station.

Achievements were celebrated with numerous prizes from F1000 and the organising committee. The symposium was concluded with a 'Spicy TR(i)P' to Masala Zone for some classic activation of TRP channels. Congratulations to all the winners and a huge thank you to all the judges for their time and assistance in reviewing the entries.

We'd like to thank all of the speakers (Professor Susan Brain, Professor Maria Belvisi, Dr Scott Earley, Dr David Andersson, Dr Anthony Albert, Dr Peter Cox & Dr Eva Amsen) and delegates for making this symposium such a success.



YLS2014 Poster Presentation session

Interactive workshop on 'New Frontiers to Publishing: Publish or Perish' by F1000

YLS2014 poster and oral prize winners: T Banke, R Clarke, A Soares, C O'Leary and H Wilson

Meeting Notes

2014 International Lecture and Pan-American Congress

2–6 August 2014,
Iguassu Falls, Brazil

Michael Spyer

Honorary member,
The Physiological Society

Carol Leandro and Joao Henrique with Mike Spyer at the Federal University of Paraiba

The award of the 2014 International Lecture to me was both an honour and surprise. I was delighted to have the opportunity to renew old friendships in Brazil and to travel to places that I had not previously visited. These visits would allow me to learn more of how physiological sciences are developing in Brazil and allow me to promote The Physiological Society. The Society was also eager for me to represent it at the PANAM 2014 Congress, the first meeting that had been organised for physiological societies from south, central and north America.

Brazil holds a very real interest for me. In the 1970s in Birmingham Pedro Guertzenstein from Sao Paulo had spent time in Sidney Hilton's laboratory and around that time I had also met Osvaldo Lopes from the same Brazilian lab in Eric Neil's laboratory. Whilst having rather different scientific views, we had become good friends. Pedro was followed by Henrique Futuro Neto who studied for his PhD in John Coote's lab developing a longstanding collaboration with Mike Gilbey that continued when Mike joined my Department at the Royal Free. From that beginning several young Brazilian physiologists passed through my London lab and in particular Karla Sampaio spent a period working on vagal preganglionic neurons in London. A significant collaboration developed between my lab and Vitoria, with the support of CAPES (the Brazilian Governments Funding Agency), the British Council and the Wellcome Trust, that facilitated exchanges.

This lecture tour represented my fifth visit to Brazil and began in Sao Paulo. My host at the Federal University was Thiago dos Santos Moreira, currently the President of the Brazilian Physiological Society. Thiago and Vagner Attunes, the treasurer of the PANAM Meeting and IUPS2017, gave me a good introduction to their labs. They are in an international competitive department and are well funded with significant funds being available from Sao Paulo State. It is a major centre for cardio-respiratory research, which is a major interest in Brazil. This is in no small measure through the importance of Benedito Machado (Ribiero Preto) who is Brazil's leading physiologist and the mentor of the majority of Brazil's young and accomplished physiologists. I had a lively audience for my lecture and had numerous engaging discussions.

I then travelled to Vitoria where my hosts were Henrique Futuro Neto and Karla Sampaio. The Federal University has developed greatly since my last visit and there has been a growing level of support from the national government. However resources are still much less than in Sao Paulo State. However the labs are very active and the department was full of enthusiastic students and post-docs. I had a very full academic visit that was supplemented by a wonderful social programme that allowed me to visit the countryside and get a feeling for the amazing variety of vegetation. The hospitality was excellent and I wished that I could have had longer to really understand the changes occurring.

The next part of the tour was PANAM 2014. Karla and her colleagues accompanied me from Vitoria, worried that alone I would have failed to negotiate the various airports *en route*. We arrived in Iguassu Falls with a day for exploration before the meeting began. The Falls are truly amazing and like most of the participants, I took a boat ride to the falls leaving looking like a drowned sheep. All the other Brits at the meeting experienced the same soaking. We also visited the neighbouring bird sanctuary. The meeting, entitled 'Physiology without borders', was attended by around 1,000 delegates of whom approximately 60% were students. The Society's two journals sponsored four symposia within the meeting, which was organised in a manner similar to IUPS 2013. The Society also provided financial support for several UK scientists. Bene Machado and his organising committee had done a really good job and the meeting was a huge success. There are now plans for this to become a regular regional meeting.

The next meeting will not be until after IUPS 2017, probably in 2019, and it is likely to be held in Chile, which was well-represented at the current meeting. I was gratified that The Society's contribution was appreciated to the extent that as The Society's representative I was included in discussions about the future of the meeting. The American Physiological Society was also very well-represented and has and will give strong support for the planned continuation of the initiative. Bene and his team gave strong evidence that even without the financial muscle and organisational support that is a strength of The Physiological Society they have the ability to cope with the difficulties that come with organising international meetings. I hope that IUPS will give them the support that they need to ensure the success of IUPS 2017 by allowing them the flexibility to limit the size and scope of the meeting to what they feel comfortable to offer.

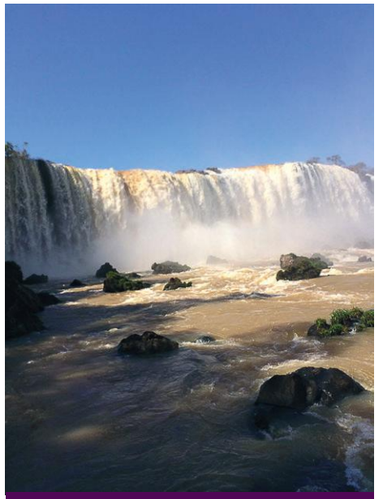
The meeting lasted for four days and I gave a talk in a symposium organised by Thiago and Dr Daniel Mulkey (USA) entitled 'New advances in the neural control of breathing' which was sponsored by *The Journal of Physiology. Experimental Physiology* sponsored a further three symposia.

Following the meeting I travelled to the north east of Brazil. This was the first occasion that I have gone so far north and it was an exciting

opportunity to learn how the reforms in education and social policy initiated by the previous President of Brazil, Dr Lula, had affected physiological teaching and research. It proved to be a revealing visit.

My first stop was in Recife where I was hosted by Carol Leandro and Joao Henrique da Silva Costa of the Federal University of Pernambuco. This is a relatively poor state and the reforms have led to a major expansion of education including the establishment of new universities in deprived areas. The university has a major campus in Recife and a second some one-hour's drive inland. The Department of Physiology is situated within an Institute of Public Health as well as having links to biomedical sciences. There is an emphasis on research into obesity which is a major national problem as in most western societies. Joao provides a physiological approach to understanding the relationship between obesity and cardiovascular disease. Carol is a leading player in major international programmes studying obesity and its social impact. Their labs were well-developed and I was impressed by the students' and academics' commitment to the ethos engendered by the reforms. As in every department that I visited in Brazil, the students were enthusiastic and showed genuine interest in discussion on my presentation and their own research.

My trip finished with a drive north to the town of Joao Pessoa in Paraiba State. Here my visit was hosted by Prof Valdir Braga who heads a thriving department in a recently established biotechnology institute in the Federal University of Paraiba. This has been supported by both government and state resources and seeks to develop novel drugs from the wide variety of plants that are unique to Brazil. The emphasis on translation does not detract from the keen determination to develop a strong basic science presence. The institute has already identified two lead compounds that will enter preclinical trials. It was clear from my visit to the north-east that the reforms have had a major impact in both socio-economic terms but also in the recognition of the importance of higher education and research in facilitating these advances. Physiology is clearly playing its part!



A small part of the majestic Iguassu Falls

We know where we are going, but how do we get there? The Society's Meetings Committee

Ken O'Halloran

Meetings Secretary,
The Physiological Society

Recently, on the pages of this fine publication, The Society's President, Richard Vaughan-Jones, rightly proclaimed a new age for our beloved discipline: a 21st century renaissance of Physiology – the science that seeks to unravel the logic of life. This timely clarion call was indeed moving, for I sat up rather too quickly and toppled my over-priced coffee-shop *Americano* as I read his wise words. As a physiologist (and as a member and elected Trustee of The Society), I have a shared responsibility for this vision. By the way, so do you reader. However, as newly elected Meetings Secretary, it dawned on me that I might actually have to take action. Crikey. I'm an academic: I don't have the requisite training! Surely there's a Committee?

Thankfully, we have that and much more: The Society's Meetings Committee. It turns out that my role is quite straight-forward. Bring these bright minds together so that we might chart the right course for The Society's voyage of discovery. Our principal aim is simple: get the science and setting right. Ay, there's the rub. But get it right and success follows because The Society's staff, members and guests deliver – time and time again. The current construct is not without its critics but few can argue with the large-scale success of recent ventures guided by my predecessor, David Wyllie, and Prem Kumar before him, working with their respective committees. Our meetings are successful, not just because we think they are. Rather, because you and others tell us so. Our meetings deliver beyond our important charitable object of promoting physiology. The Annual Meeting has meaningful impact. The newly launched Topic style format is off to a flying start with advanced plans now in place for the second instalment in the series: Ageing & Degeneration – A Physiological Perspective (Edinburgh, 10–12 April 2015).

However, our meetings come at a considerable cost to the Society's coffers. Newsflash: success is expensive. As such, there is added pressure on Meetings Committee to get it right and 'on budget'. I welcome a shared approach to how we, the Members, might respond to these challenges, harnessing the wisdom of the crowd. To that end, Meetings Committee is accessible to the membership in a number of ways: through the theme leads who provide valuable input on many aspects of the flavour of our various meetings; through the current Meetings Committee membership; or route one, directly to me. Praise endlessly flatters and it has the unfortunate consequence of maintenance of the status quo. Alas, excellence is not static. The Society must move, and be seen to move, with the times. Therefore, constructive criticism (to make use of managerial parlance), or good old-fashioned, heart-felt, considered views are especially welcome during my tenure in the hot seat of Meetings Committee. We may agree or disagree on method but I am sure we will share the same ambition for the membership. I am convinced that The Society has a wonderful sense of where we've been and where we want to go. Our meetings will define how we get there. It is said that the journey is as important as the destination. Important too that we ensure we bring everyone along.

Human metabolism and obesity: the influence of exercise

This article discusses the effects of physical activity and exercise programmes on human metabolism and obesity. It demonstrates how exercise and physical activity are important regardless of body weight or composition, and reports on a number of successful interventions including community-based exercise programmes that have reduced body fat and improved health outcome markers in overweight/obese individuals.

Dr Naomi Brooks & Dr Stuart Galloway

Health & Exercise Sciences Research Group, University of Stirling, UK

The rapid and continuing rise in obesity throughout both the developed and developing world is a current critical world health issue. Increased levels of obesity are a major challenge to public health with obesity contributing to increased cases of type 2 diabetes, cardiovascular disease, stroke, cancer and loss of quality of life. Metabolic syndrome and type 2 diabetes are also key factors influencing cardiovascular disease risk. Further, location of adipose tissue – i.e. abdominal adipose and intra-abdominal (visceral) adipose tissue – is associated with increases in the risk of cardiometabolic disease. Morbidity and mortality from cardiometabolic disease put a great burden on individuals, families and communities and put an increased financial burden on health care systems.

'Physical activity and exercise have consistently been shown to improve health outcomes in individual and group exercise programmes, albeit with varying degrees of individual responsiveness'

At its most simple, obesity is considered to be caused by increased energy intake without concomitant energy usage. However, it is not that simple. Environmental and behavioural factors including increased calorie consumption and food intake (foods high in sugar and fat) can influence the energy imbalance. Decreases in physical activity also contribute, some would argue more so, to the obesity crisis. Physical inactivity and sedentary lifestyle are independent risk factors for metabolic disorders. Adequate physical activity is required for metabolic health and acts to reduce risk factors associated with atherosclerosis and metabolic disorders, particularly rectifying high blood pressure, insulin resistance, glucose intolerance, low HDL-cholesterol, high LDL-cholesterol, and high triglycerides. Physical activity in addition to reduced sedentary time (sitting less) is therefore recommended in both prevention and treatment of these metabolic disorders.

An increased body mass, measured by body mass index (BMI: mass (kg)/height $(m)^2$), has been consistently reported to be linked to increased mortality and morbidity throughout the lifespan. The recommended BMI for a healthy individual is 18.5–24.9 kg/m^2; overweight is defined as BMI of 25–29.9 kg/m^2 and obese is defined as ≥30 kg/m^2. However, BMI does not take into consideration body composition or location of fat mass.

Obese individuals develop health complications due to an increasing number and size of adipocytes (increasing fat mass). The increased size and number of adipocytes leads to dysfunction and cellular stress which contributes to insulin resistance, increased inflammation and increases in circulating lipids (for detailed review see Capurso & Capurso, 2012). Obese individuals develop resistance to the cellular effects of insulin, which displays as an impaired ability of insulin to stimulate glucose uptake from plasma into fat and muscle cells. It is thought that increased fatty acids (FAs) combined with lipid metabolites/signalling molecules interfere with the insulin-signalling pathway and can impair the actions of insulin and contribute to

‘lifestyle interventions can be more effective than current prescription drugs for treating and preventing diabetes’

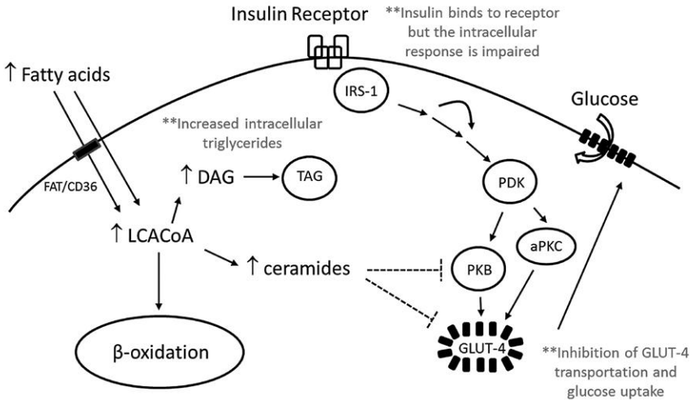


Figure 1. Insulin signalling normally increases GLUT4 translocation, but with insulin resistance this is thought to be blocked by accumulation of fatty acid metabolites such as long-chain acylCoA (LCACoA), diacylglycerols (DAG) and ceramides. That is delivery of fatty acids is greater than the capacity for oxidation and/or storage as triglycerides. Figure simplified from Timmers *et al.* (2008). More detail from the original review article.

Table 1.

	Healthy	Unhealthy	
Insulin sensitivity			
Fasting glucose	< 6 mmol/L	6–7 mmol/L *impaired fasting glucose* > 7 mmol/L *diabetes*	
Fasting insulin	1.4–14 μIU/ml		
Lipid profile			
Total cholesterol	< 5 mmol/L	> 5 mmol/L	Increased risk of cardiovascular disease
HDL cholesterol	> 1 mmol/L	< 1 mmol/L	
LDL cholesterol	< 3 mmol/L	> 3 mmol/L	
Triglycerides	< 1.7 mmol/L	> 1.7 mmol/L	
Blood pressure			
Systolic BP	120 mmHg	> 140 mmHg	Hypertension
Diastolic BP	80 mmHg	> 90 mmHg	

Definitions

Insulin sensitivity can be assessed by measuring fasting blood glucose and insulin levels and/or levels after a glucose drink (oral glucose tolerance test).

Lipid profile measures various lipids in the blood including triglycerides, total cholesterol, low-density lipoprotein (LDL-)cholesterol and high-density lipoprotein (HDL-)cholesterol).

Blood pressure is measured with a sphygmanometer and normal values are 120/80 mmHg. Hypertension is considered to be when values are above 140 and 90 mmHg, respectively.

(Healthy values are in Table 1)

Values taken from NHS Choice

insulin resistance (Fig. 1). The resistance to the action of insulin results in elevated plasma glucose concentration (see Table 1 for normal values). The pancreas continues to secrete insulin in an attempt to reduce blood glucose concentration and eventually the beta-cells fail, and individuals with type 2 diabetes then require insulin therapy.

The adipocytes themselves are not inactive cells but are extremely important in human metabolism. Adipocytes secrete metabolically active proteins (adipokines) such as leptin, adiponectin and resistin, which contribute to healthy metabolism and are altered with obesity. Alterations of adipokine secretion lead to pathological consequences such as insulin resistance and increases in plasma lipid concentration. Adipocytes also contribute to the increased systemic inflammation noted with obesity, including increases in tumor necrosis factor-α, interleukin-6 and C-reactive protein, which are associated with insulin resistance and CVD. In addition, the increase in circulating FAs and other lipids leads to increased storage of fat in other tissues such as triglycerides in skeletal muscle and liver. While an increase in fat storage in muscle provides an important fuel source for some (i.e. athletes), in others such as non-active obese individuals, this has been further linked to insulin resistance (Fig. 1). Indeed, the capacity to oxidise FA seems an important determinant of the impact of caloric excess and obesity on insulin resistance. It is now well recognised that increasing the capacity of skeletal muscle to oxidise lipids, through exercise induced increases in mitochondrial volume, can effectively restore insulin sensitivity. This effect would likely be larger if both caloric restriction and exercise were adopted.

Skeletal muscle is an extremely important metabolic tissue and uses glucose and fat as well as amino acids for energy production. Glucose is a key fuel utilised in skeletal muscle during exercise and this uptake and usage is independent of insulin action. Thus, individuals who are insulin resistant, such as those with type 2 diabetes, can reduce blood glucose by increased use of their skeletal muscle mass. Physical activity, particularly in the fasted state, can also reduce the pathological complications of metabolic dysfunction in obesity by increasing oxidation of blood borne and intramuscular FAs, reducing the impact of these FAs on insulin resistance. Chronic bouts of contraction of skeletal muscle (e.g. exercise training) lead to production of myokines and anti-inflammatory responses, which reduce reactive oxygen species, mitochondrial dysfunction and ER stress, all of which contribute to reducing metabolic dysfunction. Interestingly, there appears to be a relationship between intensity and volume of physical activity and the cardiovascular/metabolic health outcomes. Research from competitive athletes suggests that their physical activity volume is conducted predominantly at low intensity (~75–80%) and with very little at moderate exercise (~5–10%) and a larger amount at vigorous intensity (~15–20%). Adopting these activity durations/distributions can produce greater cardiovascular and metabolic adaptations (Neal *et al.* 2013) in well-trained recreational athletes, which suggests that targeting physical activity intensity at the light and vigorous intensity ends of the spectrum could be more beneficial for health. Vigorous activity produces health improvements such as reducing adiposity and risk markers of cardiovascular and metabolic diseases (e.g. increases aerobic capacity and reduces fat mass). Thus, there are strong associations between aerobic fitness, amount of vigorous activity, and adiposity that are important in reducing cardiovascular and metabolic disease risk markers.

Physical activity and exercise have consistently been shown to improve health outcomes in individual and group exercise programmes, albeit with varying degrees of individual responsiveness. While there is consistent evidence that BMI is a predictor of all-cause mortality, and therefore reducing BMI is of benefit health-wise, there are a number of paradoxes to this thinking. Of particular interest is the FIT FAT phenomenon recently reviewed by McAuley & Blair (2011), which suggests obesity is not a risk factor for mortality in fit individuals. The FIT FAT phenomenon is based on evidence that obese individuals who are fit are at no greater risk for mortality than normal weight fit individuals. However, the likelihood of being fit is also related to BMI, with higher numbers of normal weight individuals being considered to have higher fitness levels compared to overweight individuals (i.e. NHANES, Duncan *et al.* 2010). These observations further highlight the importance of exercise and particularly moderate to vigorous exercise in maintaining health, regardless of body mass or BMI. While weight loss is important to obese and overweight individuals, increasing physical activity and exercise to improve fitness is of importance to healthy outcomes regardless of weight loss. This is a key aspect often missed when interpreting results of exercise programmes and when planning interventions for improvements in health.

An excellent recent example of a successful public health intervention involving a research programme of lifestyle intervention has been running for the last 4 years in Scotland. The Football Fans in Training (FFIT) is a 12-week, gender-sensitised weight management and physical activity programme delivered to groups of men at Scottish Premier League clubs. The programme has been led by the University of Glasgow and was developed to use scientific approaches to weight loss, physical activity and diet, which are delivered to participants at their football clubs. The aim of the intervention was to encourage individuals to make lifestyle changes to reduce their risk of ill health by losing weight, becoming more physically active and consuming a healthier diet. Individuals were recruited from football clubs throughout Scotland. After a successful pilot study (Gray *et al.* 2013) showed that the 12-week intervention was feasible and can have a positive effect on lifestyle choices, reduced obesity and increased physical activity, the project was expanded to include football clubs throughout Scotland.

The recent report on this study published in *The Lancet* (Hunt *et al.* 2014) details a follow-up of the 747 individuals who took part in the 12-week FFIT programme. Each week participants had one 90-minute session, which included combined advice on healthy diet with physical activity. After 12 weeks, average mass loss was 5.8 kg, waist circumference reduced by 6.7 cm, BMI by 1.9 kg/m^2, body fat percentage by 3%, systolic BP by 8 mmHg and diastolic BP by 4 mmHg (all statistically significant). Improvements were reported in dietary intake with reduced fatty food intake, sugary food score, and alcohol consumption, and increased fruit and vegetable score (all significantly different from baseline). The 12 month follow-up reported waist circumference reduced from baseline by 7.3cm, BMI reduced by 1.8 kg/m^2, body fat percentage by 2%, systolic BP by 8 mmHg and diastolic BP by 5 mmHg (all statistically significant). The alterations reported in diet were maintained at 12 months. Significant increases in self-esteem, mental and physical health, and quality of life were all noted after 12 weeks and remained higher than baseline at 12 months. The FFIT programme has been hugely successful at encouraging lifestyle changes and increases in physical activity for overweight and obese men. Furthermore, the study targeted a population who are generally reluctant to join exercise programmes, and there was a 90% retention of individuals in the programme – a key point in its ongoing success.

Another older success story of the positive effects of exercise and lifestyle changes on metabolic health is reported with the Diabetes Prevention Program, a large randomised clinical trial involving individuals who were at risk for developing type 2 diabetes in the USA (Knowler *et al.* 2002). The aim of the study was to investigate whether lifestyle intervention or treatment with metformin (a popular drug to treat diabetes) could prevent or delay the onset of diabetes. Participants in the study were at risk for type 2 diabetes, with BMI of ≥24 kg/m^2 and fasting plasma glucose of 5.3 – 6.9 mmol/L. Individuals in the study were randomly assigned to one of three interventions: standard lifestyle recommendations with metformin (initially 850 mg once/day and increased to 850 mg twice/day after 1 month); standard lifestyle recommendations with placebo; or an intensive programme of lifestyle modifications. The intensive programme of lifestyle modifications involved

a 16-lesson curriculum containing diet, exercise and behaviour modifications. The goal was to achieve and maintain a 7% weight reduction through low-calorie, low-fat diet and engage in physical activity of moderate intensity for at least 150 minutes/week. The study included 3234 individuals (average age 50.6 ±10.7 years) and the average follow-up was 2.8 years. At follow-up, the placebo group had incidence of diabetes with 11.0 cases/100 person years. The group given metformin had a reduced incidence of diabetes (7.8 cases/100 person years; 31% lower). However, the lifestyle intervention group had a significantly lower incidence of diabetes than both the placebo and the metformin group (4.8 cases/100 person years; 58% lower). The results show that individuals in the lifestyle group decreased energy intake by ~450 kcal/day and increased physical activity to the greatest degree. Thus, lifestyle interventions can be more effective than current prescription drugs for treating and preventing diabetes.

Finally, there has been a lot of recent attention on short-term high-intensity interval training (HIIT) and the benefits to metabolic health. Skeletal muscle is highly adaptable to exercise and short-duration high-intensity exercise bouts can significantly improve skeletal muscle metabolism. It appears that the disturbance in homeostasis at exercise onset, i.e. the beginning of a HIIT session, or the high rate of utilisation of glucose/glycogen is fundamental for upregulation of key regulators in skeletal muscle fat and carbohydrate metabolism. Thus, repeated rest-to-exercise transitions, which occur over a short period, appear to be a beneficial way to increase whole body fat metabolism. Adopting this approach in seven high intensity interval training sessions over 2 weeks led to an increase in whole body fat oxidation during exercise by 36%, and increased skeletal muscle capacity to oxidise FAs in women (Talanian *et al.* 2007). This type of exercise intervention has been reported to have great promise for individuals with impaired metabolic responses and has been shown to increase fat metabolism and reduce body fat stores in obese individuals. Alternatively, sprint interval training has also been shown to have similar effects on skeletal muscle metabolic adaptation in a time efficient manner (reviewed in Gibala *et al.* 2012). Furthermore, Gibala *et al.* (2012) discuss in detail how HIIT training has been used effectively to improve cardiorespiratory fitness in individuals at risk for CVD and metabolic disease.

In addition to the positive influences of exercise, dietary restriction and associated mass loss remain influential in the pursuit for health and reduction in obesity and consequential effects. A promising recent study reports evidence that the beta-cell dysfunction and insulin resistance characterised in type 2 diabetes can be reversed (Lim *et al.* 2011). The project undertaken at Newcastle University investigated the effects of a very low energy intake (600 kcal/day) on type 2 diabetes. Participants had type 2 diabetes (age 49.5 ± 2.5 years) and BMI of 33.6 ± 1.2 kg/m^2. After 1 week of energy restriction, fasting plasma glucose concentration normalised to 5.9 mmol/L and remained stable throughout the 8-week study. Beta-cell function and hepatic insulin sensitivity were both restored to healthy function within the 8-week study timeframe. Average mass loss was 15 kg. These data clearly demonstrate the power of short-term reductions in energy intake alone, but exercise in combination with diet restriction would ensure healthy body composition changes to help retain lean mass while losing fat mass.

In summary, increasing physical activity and exercise, even in individuals who are obese, can have beneficial effects on reducing risk of mortality, increasing/maintaining muscle mass and improving metabolism in the face of mass loss, as well as overall health and wellbeing. The present article provides a very brief overview of a number of studies highlighting that provision of community based exercise programmes and appropriate lifestyle interventions are feasible and can be extremely beneficial for health outcomes in obese individuals. We have recently presented similar findings of a community-based exercise intervention in women from previously disadvantaged backgrounds in South African townships, demonstrating improvements in metabolic health are also observed in these individuals. Our data also demonstrate that community-based exercise programmes are feasible and effective in the South African township setting (Brooks *et al.* 2014).

It is clear from the details presented that there are a variety of ways to improve metabolic health including volume and intensity of exercise as well as dietary modification. While it is widely acknowledged that exercise is beneficial, we do not yet understand the optimal approach to exercise interventions. Perhaps the bigger question is how to maintain people in exercise programmes, which tend to have a large dropout rate. The Scottish FFIT programme provides evidence that retention and longer term behavioural changes are certainly possible in hard to reach groups when the correct approach is taken. It is clear that physical activity and exercise are beneficial for obese individuals with or without associated weight loss. As such, it is fundamental to incorporate a variety of exercise programmes and use the expertise of health scientists, exercise physiologists, behavioural change experts and nutritionists/dieticians when designing and implementing an exercise programme or physical activity intervention.

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Exercise: more than just a role in energy balance

Improving our understanding of the mechanisms by which physical exercise enhances health requires physiologists to isolate the relative effects of exercise *per se*.

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Research studies investigating the impact of exercise on health often show physical activity/exercise to be beneficial. However, energy status (deficit, balance, surplus) can have a profound impact on metabolism. To understand whether exercise leads to health improvements, energy balance needs to be carefully controlled.

Numerous studies have shown that regular exercise can have beneficial effects on metabolic function and various other health markers. Over the last decade, there has been a prolonged debate about whether the effects of exercise are simply secondary to the role of exercise in energy balance. Whether exercise offers additional benefits compared to diet alone remains unclear – which makes it difficult to provide clear guidance to the public and healthcare professionals. If exercise is only important because of a role in energy balance then, arguably, the greatest emphasis and focus should be on adiposity as the key outcome – irrespective of the route via which weight loss or weight maintenance has been achieved (i.e. diet or exercise). In this context, one historical problem is that many exercise studies fail to adequately control energy balance in order to unpick the relative effects of exercise *per se*. For example, if a group of individuals are trained for several weeks during which they lose several kilograms of adipose, it will remain unclear which physiological events were primary in driving any observed changes (i.e. exercise, energy balance or loss of adipose). To understand and isolate how exercise exerts its effects on metabolism, it is important to conduct studies that will tease apart the effects of energy balance and weight loss from exercise/physical activity, while carefully controlling energy status (Braun & Brooks, 2008).

> 'The combination of short-term overfeeding and reduced physical activity had a dramatic impact on insulin sensitivity'

Some excellent studies have already started to unpick the relative importance of exercise in the context of an energy deficit. For example, work by the CALERIE team at Pennington has used sophisticated designs where weight reduction was achieved either through caloric restriction alone, or through a combination of caloric restriction and increased structured exercise. The energy deficit elicited was matched between groups leading to similar changes in body mass and composition (Redman *et al.* 2009). While this study suggested that exercise plays an equivalent role to caloric restriction in terms of energy balance, another study by the same group showed that exercise combined with caloric restriction did further improve metabolic function compared to caloric restriction alone (Larson-Meyer *et al.* 2010). Although understanding the contribution of physical exercise during a period of energy deficit or energy balance is extremely helpful in the context of weight loss, it is only part of the picture. It is likely that most individuals intermittently experience brief periods of positive energy balance and experimental studies focusing on the impact of exercise and physical activity during periods of energy surplus might be equally relevant.

One of our recent papers published in *The Journal of Physiology* took a very different approach with striking results (Walhin *et al.* 2013). In this study, 26 healthy young men

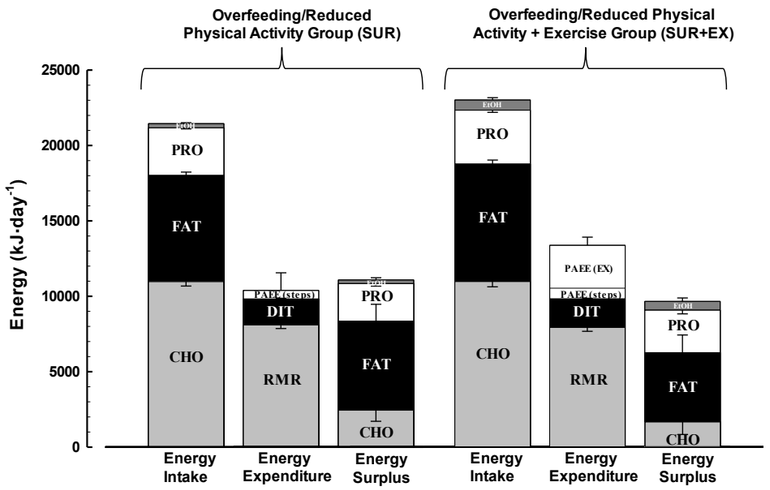

Figure 1. Schematic representation of the energy surplus achieved by the overfeeding and restricted physical activity model in both groups. CHO = Carbohydrates; PRO = Protein; EtOH = Alcohol; RMR = Resting Metabolic Rate; DIT = Diet Induced Thermogenesis; PAEE = Physical Activity Energy Expenditure. Values are means ± CI

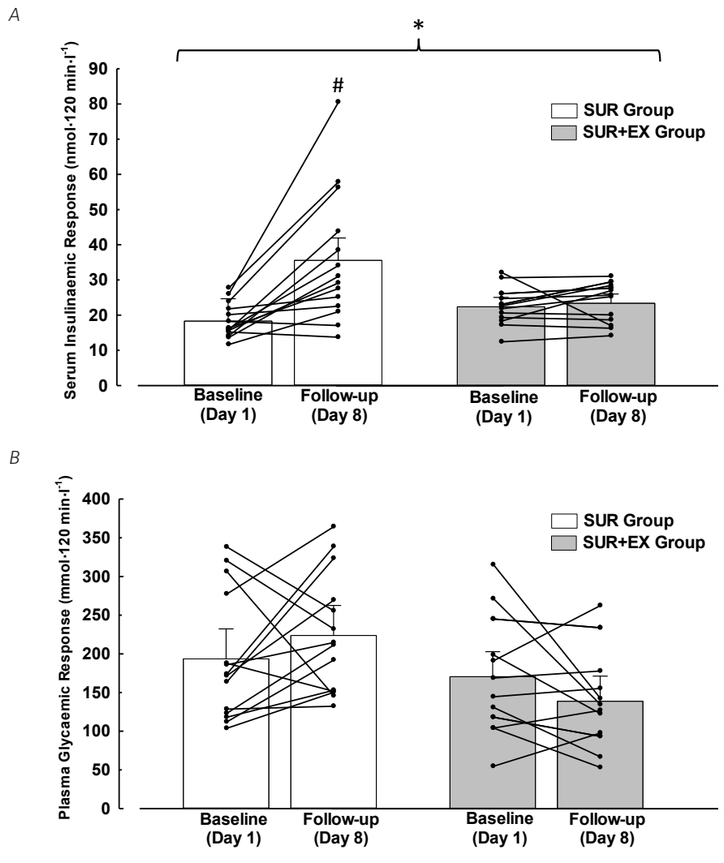

Figure 2. Serum insulin 2h iAUC (*A*), plasma glucose 2h iAUC.(*B*); means ± CI) in response to the OGTT before and after a week of overfeeding and reduced physical activity. In *A*, * denotes a dayxgroup interaction ($P = 0.002$); # denotes values different pre-post within SUR group ($P = 0.001$).

reduced their physical activity to sedentary levels (≤ 4000 steps per day) for 7 days. Half of the group performed a daily bout of vigorous-intensity treadmill running for 45 minutes. Everyone was asked to over-consume their habitual diet: the non-exercising group (SUR group) increased their energy intake by 50%, whilst the exercising group (SUR+EX group) increased their energy intake by 50% plus the energy expended during the exercise (so the net energy surplus was matched in both groups). After one week and a surplus of around 17,000 kilocalories, serum insulin responses to glucose ingestion and biopsies of adipose tissue were taken. Results showed that participants from both groups gained weight during the course of the intervention. Fig. 1 shows the matched energy surplus induced in both groups.

The combination of short-term overfeeding and reduced physical activity had a dramatic impact on insulin sensitivity (Fig. 2). We demonstrated that after just 7 days of positive energy balance, fasting insulin concentrations increased and the ingestion of 75 g of glucose resulted in a ~2-fold increase in the insulinaemic response of healthy individuals. Our calculations suggest that excess carbohydrates would have resulted in a saturation of skeletal muscle and liver glycogen stores. It is likely this contributed to a decrease in insulin sensitivity. Remarkably, the inclusion of a daily vigorous-intensity exercise bout largely prevented these changes from taking place even though extra food was provided to the participants in order to keep the energy surplus the same between groups. Thus, even though the SUR+EX group consumed even more energy in order to match the energy surplus of the SUR group, they were still better off at the end of the week.

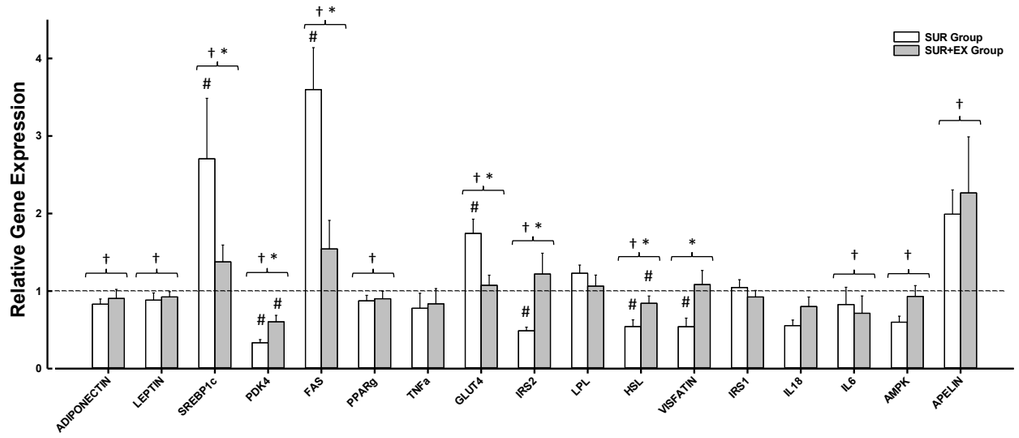

Figure 3. Relative gene expression of several key genes measured in adipose tissue at baseline and follow-up for the SUR group ($n = 10$) and the SUR+EX group ($n = 12$). Dashed line represents no change. Data normalised to PPIA, baseline and internal calibrator. Values are means ± SEM. *$P \leq 0.05$ dayxgroup interaction. #$P \leq 0.05$ baseline versus follow-up. †Main effect of day (i.e. Day 1 vs. Day 8 both groups; $P \leq 0.05$).

Surprisingly few studies have focused on changes in the expression patterns of key genes in adipose tissue during a bout of energy surplus in healthy individuals, considering it is the major site for energy storage. The experimental model used in this study had a significant impact on the expression of several key genes within adipose tissue (Fig. 3). For example, overfeeding and reduced activity significantly increased the expression of both SREBP-1c and FAS transcripts in the SUR group. SREBP-1c is a transcription factor that regulates the expression of the lipogenic enzymes FAS. It is likely that the protocol used would have rapidly saturated liver and muscle glycogen stores favouring a lipogenic environment. The SUR group had little capacity for carbohydrate oxidation as a result of restricted physical activity. SREBP-1c has been linked with *de novo* lipogenesis (DNL) which has been shown to take place in adipose tissue, thus providing a route for the disposal of excess glucose. Other genes and proteins such as PDK4, HSL, IRS2 and AMPK were down-regulated, highlighting a switch of oxidative fuel from fatty acids to glucose. It is possible that these changes within adipose tissue may be a secondary response to the marked hyperinsulinaemia resulting from the positive energy balance induced by the overfeeding and reduced physical activity – although as we discuss in the full paper there are a number of other possibilities. It is particularly interesting that exercise exerted pronounced effects in adipose tissue, even whilst it was expanding (i.e. whilst people were gaining weight).

This study provides some of the strongest evidence to date that the picture is far more sophisticated than simply understanding the contribution of exercise towards energy balance alone. Exercise has positive effects even when we are actively storing energy and gaining weight. Interestingly, exercise has a powerful impact in adipose even when energy is being actively stored within this specific tissue. This is rather reassuring because even a large amount of exercise plays only a relatively modest role in overall energy balance (Turner *et al.* 2010). The fact that this nonetheless exerts powerful physiological effects supports a justifiable focus on exercise (independent of its role in energy balance and the regulation of adiposity).

While the model used here might seem extreme to many readers, it is strikingly similar to what many of us experience at particular times of the year (Hull *et al.* 2006). Incidentally, the journal article was published towards the end of last year around Thanksgiving and Christmas which created enormous media interest. Newspapers such as *The New York Times*, *The Telegraph* and *Le Monde* picked up on the findings and the article in *The New York Times* was one of the most read stories on their website for a few days. Maybe the fact most people can relate to these findings is part of the reason this study created such interest. This was reflected in some of the headlines: 'Daily exercise can help ensure guilt-free Christmas', 'Workout "cuts festive food damage", 'Exercise allows "healthy overeating" during holidays: daily workouts offset metabolic disruption, nutritional imbalance'. Of course, further work is required to establish whether these findings would be valid in the longer term and whether other forms of exercise varying in intensity and duration would provide the same benefits.

In summary, the experimental model that we used in our paper in *The Journal of Physiology* successfully enabled us to tease apart the relative importance of exercise independent of energy balance. These results demonstrate that exercise has powerful effects on physiological function even in the face of a considerable energy surplus and whilst people are actively gaining weight. This study adds to the evidence that we should not just be looking at exercise as a route to achieve energy balance and weight loss, but also because it can have profound physiological effects. The emphasis should not just focus on body mass alone, but also on the behaviour (exercise).

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Sleep disturbance alters autonomic balance to the heart

Sleep disturbances such as sleep apnoea can cause a chronic imbalance in the autonomic nervous system, and if left untreated, can lead to cardiovascular diseases.

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Sleep disturbances, including obstructive sleep apnoea (OSA), are very common causes of cardiovascular diseases. For example, OSA, prevalent in ~24% of adult males and ~9% of adult females (between 30 and 60 years of age) (Young *et al.* 1993), is characterized by chronic repetitive interruptions of breathing during sleep. These episodic periods with suspensions of breathing (apnoea) cause cycles of combined hypoxia (low oxygen) and increases in CO_2 levels (hypercapnia) that often brings the person to a lighter state of sleep or brief wakefulness to stimulate and restore normal breathing. Left untreated, OSA may generate, and/or maintain, many cardiovascular diseases, including hypertension, arrhythmias and sudden cardiac death.

One of the key consequences of OSA is a chronic imbalance in the autonomic nervous system, which serves to maintain homeostatic cardiovascular function as well as to protect against challenges and perturbations to the cardiovascular system. Both the sympathetic and parasympathetic divisions of the autonomic nervous system regulate neural control of the heart, with parasympathetic activity dominating this balance. A normal resting heart rate of ~60–80 beats/minute is maintained by the tonic parasympathetic activity to the heart, without which heart rate would become elevated (~100 bpm) with a higher risk of arrhythmias. While previous work by others has focused on how OSA elicits sympathetic overactivity, the goal of the current study was to study and identify the mechanisms responsible for diminished cardioprotective parasympathetic control of heart rate in OSA. To accomplish these goals we utilised an animal model of chronic intermittent hypoxia–hypercapnia (CIHH) that mimics OSA in humans, and examined the critical synaptic pathways to neurons that generate the parasympathetic activity to the heart.

Parasympathetic cardiac vagal neurons (CVNs) of the brainstem, located in nucleus ambiguus and dorsal motor nucleus of the vagus, generate the parasympathetic activity to the heart. The vagal descending projections from these neurons synapse upon postganglionic intracardiac ganglia neurons located in close proximity to the heart (Mendelowitz, 1999). CVNs are intrinsically silent and hence their activity is dictated by the excitatory (glutamatergic) and inhibitory (GABA and glycinergic) synaptic activity arising from other regions of the brain (Mendelowitz, 1996) (Fig. 1).

A functional deficit in the brainstem circuitry responsible for parasympathetic activity to the heart (Gu *et al.* 2007), especially activation of CVNs (rather than anatomical or functional changes in peripheral innervation of the heart (Lin *et al.* 2007; Yan *et al.* 2008)) is responsible for impaired parasympathetic control of the heart with chronic intermittent hypoxia (CIH).

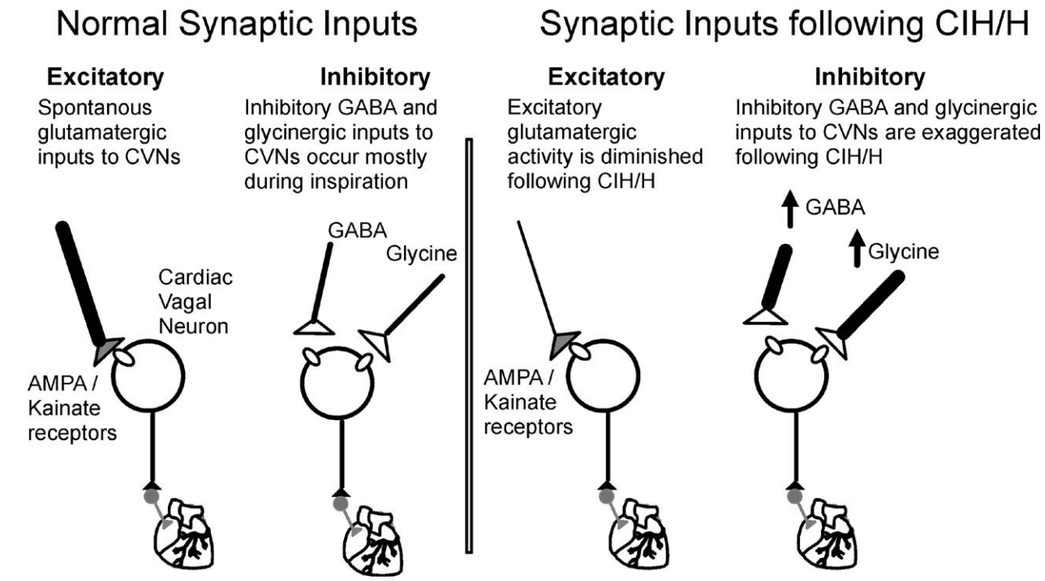

Figure 1. Cardiac vagal neurons (CVNs), which supply the parasympathetic activity to the heart, normally receive sufficient excitatory glutamatergic synaptic inputs to initiate and drive their activity, as well as inhibitory GABAergic and glycinergic inputs that modulate their firing, particularly with the respiratory rhythm; see left panel. However, following chronic intermittent hypoxia–hypercapnia, a model of sleep apnoea, the excitatory glutamatergic activity is diminished while inhibitory GABA and glycine neurotransmission to CVNs becomes exaggerated (right panel).

Supporting the hypothesis that CIH impairs CVN function in the brainstem, the heart rate response evoked upon microinjection of glutamate (Yan *et al.* 2008), into the nucleus ambiguus, where CVNs are located, is diminished by CIH. However, beyond alterations in glutamate receptor density little was known about how CIH impairs CVN function and what, if any, targets can be identified to restore cardioprotective parasympathetic activity to the heart.

The changes responsible for diminished vagal control of heart rate were identified by studying the changes in blood pressure, heart rate and neurotransmission to CVNs evoked by acute hypoxia–hypercapnia and CIHH. The methods have been described in detail in (Dyavanapalli *et al.* 2014). Briefly, *in vivo* telemetry recordings of blood pressure and heart rate were obtained in adult rats prior to and during 4 weeks of CIHH exposure. CIHH exposures were performed by placing the rats in commercial atmosphere controlled chambers, exposed to repetitive cycles of 3 minutes of mild hypoxia–hypercapnia (6% O_2 + 5% CO_2 + 89% N_2) followed by 3 minutes of normoxia (21% O_2 + 79% N_2), repeated for 10 times/h, 8 h/day, for 4 weeks during the light phase. Fluorescently labelled CVNs were visualised and identified in an *in vitro* brainstem slice preparation obtained from adult rats exposed to either air or CIHH for 4 weeks. Neurotransmission to CVNs, including postsynaptic inhibitory and excitatory synaptic events, were recorded using whole cell voltage clamp techniques.

Our results have shown that chronic intermittent hypoxia–hypercapnia exposure for 4 weeks increases blood pressure to hypertensive levels and blunts cardiovascular reflexes in response to both acute hypoxia–hypercapnia and CIHH. This likely occurs by the observed changes in the neurotransmission to cardiac vagal neurons that normally maintain a low resting heart rate. Specifically, cardiac vagal neurons received an increased frequency of inhibitory (both GABA & glycinergic) and depressed incidence of excitatory (glutamatergic) neurotransmission with CIHH. These changes would act in concert to inhibit the activity of CVNs and diminish cardioprotective parasympathetic activity to the heart. These alterations of cardiorespiratory network function within the brainstem would contribute to the increased heart rate, blood pressure and risk of adverse cardiovascular events that occur in patients with OSA.

In addition to identifying the adverse alterations responsible for reduced parasympathetic activity to the heart following CIHH, the results from this study would predict that patients who have OSA and take sleep promoting medicines that typically act by enhancing inhibitory GABAergic neurotransmission within the CNS might be at heightened risk for a more significant reduction of critical parasympathetic neuronal activity to the heart. This study also provides a foundation for the development of potential therapeutic interventions to restore cardioprotective parasympathetic activity to the heart in patients with OSA.

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The mighty protein: insulin-like growth factor type 1

IGF-1 plays a critical role in skeletal muscle growth during development, muscle regeneration and muscle hypertrophy in response to training.

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Muscle atrophy and weakness are common clinical phenomena observed following bed rest, surgery, cast immobilization and injury or disease. The consequences of loss of muscle function are far reaching and include decrease of motor control and overall fitness, development of functional limitations and impairment, and long term disability. The recovery of muscle strength and function following injury or disease is a major challenge in rehabilitation.

'Administration of growth hormone has been used successfully in elderly to increase IGF-1 levels and prevent atrophy during catabolic diseases or following hip fractures'

The ability to manipulate muscle adaptation and growth has great potential in clinical situations where functional ability and strength are compromised. Administration of growth hormone (GH) has been used successfully in elderly to prevent atrophy during catabolic diseases or following hip fractures (Van der Lely *et al.* 2000). GH administration in these populations resulted in increased insulin-like growth factor 1 (IGF-1) levels, and increased muscle mass and functional ability. IGF-1 plays a critical role in skeletal muscle growth during development, muscle regeneration and muscle hypertrophy in response to training. Several growth factors have been implicated in directing muscle specific gene expression; however, the hypertrophic effects of growth hormone have been thought to be primarily mediated via IGF-1.

IGF-1

IGF-1 was first identified in 1957. It was known by other names including sulfation factors, non-suppressible insulin-like activity, multiplication stimulating activity and somatomedins. It was initially identified on the basis of three unique properties: its mediation of the skeletal growth-promoting actions of GH, its mitogenic properties, and its mimicry of the actions of insulin. This peptide was isolated in Zurich by Rinderknecht and Humbel on the basis of its insulin-like activity, but was renamed IGF-1 when it became apparent that its growth-promoting properties were more important than their insulin-like activities (Rinderknecht & Humbel, 1978).

The IGF-1 system includes ligand IGF-1, its receptor, IGF-binding proteins (IGFBPs) and IGF proteases. The biological significance of the IGF-1 was most strikingly demonstrated when its expression was 'knocked out' by homologous recombination techniques. Virtually every component of the IGF-1 system (the various ligands, receptors and binding proteins) has been knocked out, and the results demonstrate that the IGFs are very important in muscle growth and development. Indeed, a common observation in mouse lines lacking IGF-1 (and/or its receptor) is that embryonic development is impaired but embryos are viable. However, the pups die immediately after birth because they cannot breathe. The central importance of IGFs to muscle development is emphasized by the fact that mice in which expression of myogenin has been knocked out show the same result; i.e. there is essentially no functional muscle development in the absence of either IGF-1 or myogenin. The mice with an inactive IGF-1 gene studied by Powell- Braxton *et al.* (1993) were 'characterized by underdevelopment of muscle tissue,' and a 'generalized organ hypoplasia... including the muscles'. The essential role of IGFs in cell growth is shown by the report that fibroblasts from IGF-1 receptor knockout mice grew very slowly in culture unless they were transfected with a plasmid expressing the IGF-1 receptor. Using the opposite approach in which transgenic animals overexpressed IGF-1, Mathews *et al.* (1988) found that muscle and bone growth were increased approximately 30% when circulating levels of IGF-1 were 50% above control values. There was a substantial increase in weights of spleen, pancreas, brain, and kidney and an increase in DNA content of these tissues. All of these observations are consistent with the view that IGF-1 plays an essential role during normal growth and development. In spite of the association of excess IGF-2 with tumours, in general it is clear that IGF-1 plays a major role in development, growth, cell differentiation, and maintenance of skeletal muscles, both in culture and in intact animals. Most, if not all of these actions are mediated by the IGF-1 receptor, and they are strongly modulated by IGF binding proteins.

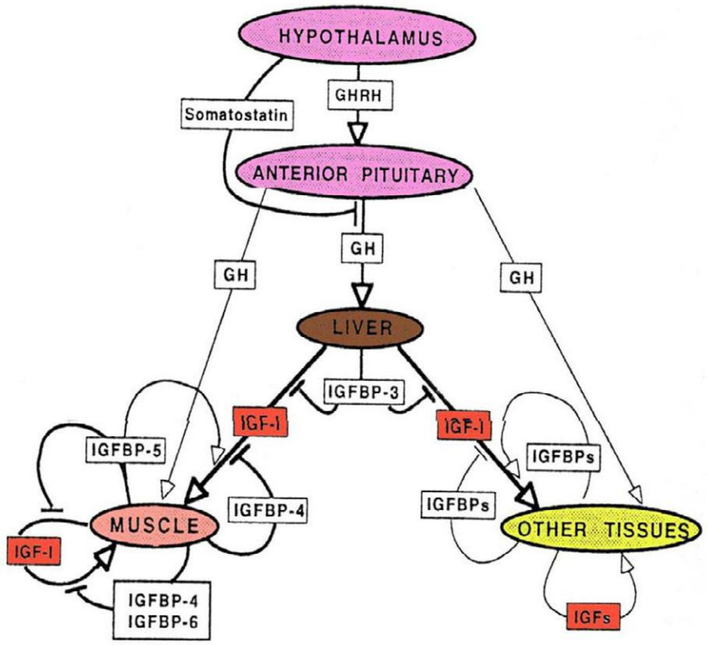

Figure 1. GH/IGF-1 axis. *(Courtesy of Dr H Lee Sweeney at University of Pennsylvania)*

Viral-mediated IGF-1 gene transfer

Increasing blood hormone levels may be risky. Specifically, the long-term safety of the activation of GH/IGF-1 levels remains uncertain with regard to tumour growth, as most human solid cancers express IGF-1 receptors. Elevated GH levels have also been linked to impaired glucose tolerance, hypertension and fluid retention. However, given the known autocrine/paracrine actions of IGF-1, local manipulation of IGF-1 expression and secretion by muscle fibres may not only be safer but also more effective (Fig. 1). Recent developments in genetic manipulation are appropriate for the introduction of small regulatory factors, such as IGF-1, into tissue. The recombinant adeno-associated virus (rAAV) vector system consists of rAAV inverted terminal repeats (ITRs) that are necessary and sufficient for replication and packaging of the virus. rAAV lacks virally encoded genes, and therefore can be used to infect adult tissue without rendering an immune response. Viral-mediated gene delivery of IGF-1 has been shown to enable efficient transfer of IGF-1 into both young and adult animals. The rAAV-virus is introduced via direct injection into a muscle compartment and endocytosed by muscle cells (Fig. 2).

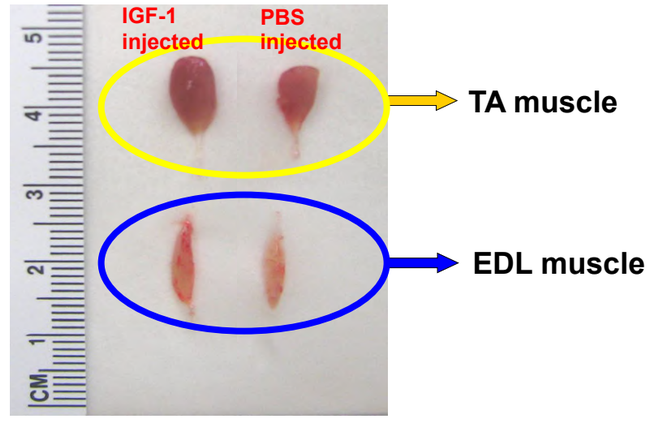

Figure 2. Visible increases in muscle mass after virus mediated IGF-1 injection into the anterior part of the mouse hindlimb. (TA= tibial anterior, EDL= extensor digitorum longus)

IGF-1 and muscle

Numerous *in vitro* studies have shown that exposure of mammalian muscle cells to IGF-1 promotes myogenic proliferation and differentiation as well as protein synthesis. Other studies have shown that administration of IGF-1 induces an increase in muscle protein content and reduces protein degradation. By injecting the gene-virus package into the muscles of adult mice, we (Ye *et al.* 2013; Stevens-Lapsley *et al.* 2010) have shown that virally mediated gene transfer of IGF-1 increases muscle size under normal loading/activity conditions (Fig. 3), but that this newly established homeostasis is maintained during cast immobilization, when neuromuscular activity is minimal. Interestingly, despite increased expression of IGF-1, the relative rate of loss of muscle mass and strength is not attenuated in virus-injected versus control muscles. We speculate that the latter is related to a decrease in IGF-1 bioactivity in the absence of neuromuscular activity, due to alterations in receptor density, binding protein, or postreceptor events. Allen *et al.* (1999) previously postulated that the level of neuromuscular activity affects the expression

‘One of the more interesting recent developments in the IGF-1 story has been the identification of a unique IGF-1 isoform that is expressed in response to changes in the loading state of skeletal muscles’

of the IGF-1 receptor (IGF-1R), making atrophying muscles less susceptible to the effects of endogenous IGF-1. Conversely, during hypertrophy, increased levels of muscle activation and loading may result in greater IGF-1R expression. Finally, we demonstrate that successful gene transfer of IGF-1 increase the muscle’s regenerating capacity. Histological examination of EDL muscles during cast-immobilization and reloading showed an increased number of central nuclei, Pax7 and embryonic myosin in IGF-1 injected muscles during reloading (Fig. 4). The presence of central nuclei and Pax7 in adult myofibres is indicative of recent fusion of activated satellite cells to existing myofibres. IGF-1 has multiple targets in muscle. IGF-1 receptors are found on activated satellite cells, adult myofibres, motor neurons and Schwann cells. Satellite cells, which retain their mitotic capacity, serve as the pool of myonuclei necessary for muscle enlargement. Satellite cells are mobilised in response to increased neuromuscular activity (activity or loading) and injury. Following activation, the satellite cells proliferate, differentiate and fuse with adult myofibres, leading to an increase in fibre size.

One of the more interesting recent developments in the IGF-1 story has been the identification of a unique IGF-1 isoform that is expressed in response to changes in the loading state of skeletal muscles. In both human beings and rats, the IGF-1 gene spans more than 70 kilobases and consists of six exons and at least five introns. Splicing is a complex mechanism by which exons are cut and pasted in different combinations from pre-mRNA. In humans, alternative splicing of IGF-1 pre-mRNA leads to the production of three different transcripts at the 3’ end, resulting in different E-peptides. It is the IGF-1Ec splice variant which has been most closely associated with stretch overload and damage, hence its being termed ‘mechano growth factor’ (MGF). However, using a viral construct and a myosin light chain (LC3f) promoter, Barton *et al.* (2006) showed that both the MGF and IGF-1Ea gene transfer could increase muscle IGF-1 (mature) expression without increasing circulating IGF-1. It appears that skeletal muscles produce both a generalized tissue-type IGF-1 and the loading-sensitive MGF isoform with differing time courses, suggesting distinct roles for these two growth factor isoforms. Expression of both IGF-1 and MGF appears to be very sensitive to the loading state of the muscle.

IGF-1 and motor neuron

The importance of IGF-1 in motor neuron survival and motor regeneration is quickly emerging. A critical role for IGF-1 in motoneuronal survival has been demonstrated during embryonic and early postnatal life, as well as in spinal cord pathology. *In vivo* studies show that IGF-1 not only inhibits neuronal cell death, but also stimulates nerve regeneration in crushed or freeze-injured nerves. Rabinovsky *et al.* (2003) found that after a sciatic nerve crush injury in transgenic mice expressing the human IGF-1 transgene, there is an increase in the number of neurofilaments staining the axons in muscle and an accelerated return of nerve conduction velocity. Similarly, IGF-1 increases intramuscular nerve sprouting 10-fold when administered subcutaneously to normal adult rats (Caroni & Grandes, 1990). Finally, IGF-1 has also been linked to age-related alterations in neuromuscular innervation (Payne *et al.* 2006). These data indicate that IGF-1 plays an important role in mature motoneuron maintenance, both in the normal state and under conditions where motor neuronal loss is found such as ageing and pathological conditions involving the central nervous system.

It has been shown that rAAV is retrogradely transported from presynaptic terminals of projecting neurons through the entire length of the axon. Kaspar *et al.* (2003) took advantage of the retrograde transport ability of AAV in a mouse model of amyotrophic lateral sclerosis and injected AAV into respiratory and motor limb muscles to directly target the motoneurons and test the efficacy of two neurotrophic factors, IGF-1 and glial cell line-derived neurotrophic factor (GDNF). They showed that IGF-1 delays the onset of behavioural symptoms and sustains life to a greater degree than GDNF. The marked effects of IGF-1 on onset and survival were accompanied by preserved morphology of motoneurons.

Conclusion

Collectively, these findings demonstrate that IGF-1 is a central trophic growth factor, essential for muscle regeneration and hypertrophy, and motor neural maintenance and regeneration. Given the role of IGF-1 in the regeneration of nerve and muscle, it is worth further investigating the therapeutic potential of overexpression of IGF-1 in different neuromuscular diseases.

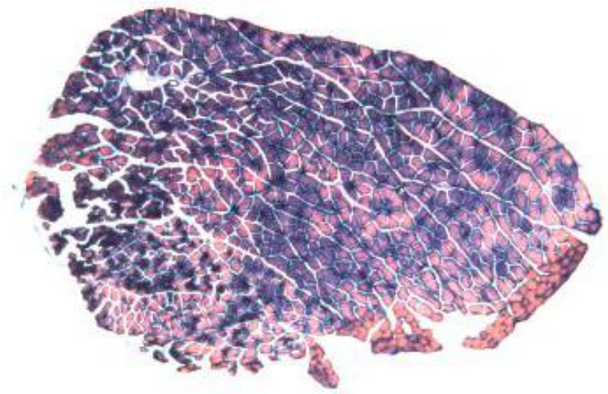

Figure 3. The efficiency of AAV gene transfer. 95–99% of EDL muscle fibres showed expression of reporter gene (LacZ) delivered by AAV1.

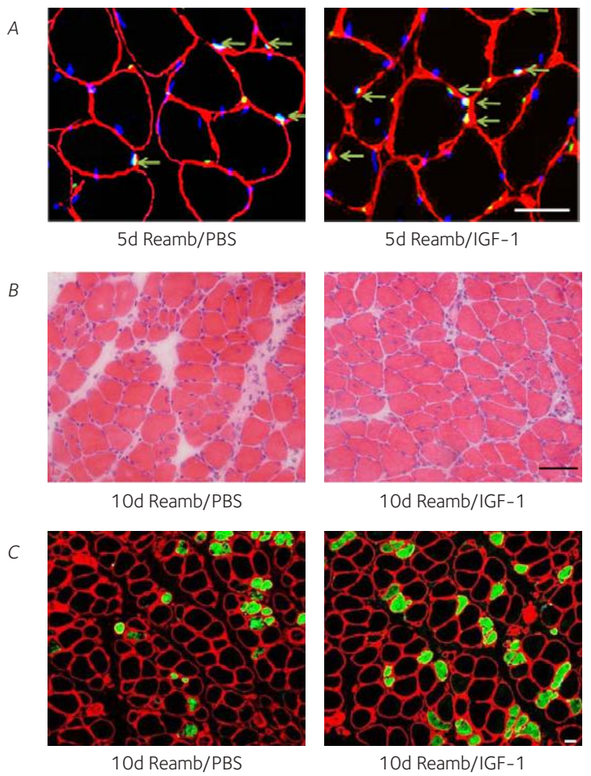

Figure 4. Markers of regeneration in the soleus across all experimental timepoints. *A*, cross-sections of the soleus muscle stained with laminin (red) + DAPI (blue) + Pax7 (green). Pax7 positive fibres (arrows) at 5 days of reloading (5d Reamb). Bar = 12.5µm. *B*, light microscopy of H&E-stained myofibres with central nuclei at 10 days of reloading (10d Reamb). Bar = 50µm. *C*, cross-sections of the soleus muscle stained with monoclonal antibody against embryonic myosin isoform (green) at 10 days of reloading. Bar = 12.5µm.

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Secrets of life from beyond the grave

"The story of how humans and all living things came into existence is told in two widely believed versions: the Book of Genesis and Darwin's Origin of Species. It was the philosopher Karl Popper who presented us with a third story, no less important." (Niemann, 2014)

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The title of the special issue of *The Journal of Physiology* on 1 June 2014 reflected the theme of the opening of the 2013 IUPS Congress: *physiology moves back onto centre stage* (Noble *et al.* 2014). The articles focus on ways in which new and often controversial developments in evolutionary biology have opened the door to the discovery of physiological functions, which play a role in determining the variations in inherited characteristics on which natural selection may act. This is known as Lamarckian heresy, which the founders of Modern Synthesis (neo-Darwinism or Synthetic Theory of Evolution) sought to exclude. But did we really have to wait until 2014 for all that to happen?

A recent book by Niemann (2014) shows that if history had taken a slightly different turn three decades ago the answer might well have been 'no'. On 12 June 1986, the great logician and philosopher of science, Karl Popper, gave the first Medawar Lecture in honour of the Nobel laureate Peter Medawar. Popper was well known for his magisterial *Logic of Scientific Discovery* and *The Open Society and its Enemies*. Very few people know that he was also deeply involved with a group of scientists, including JBS Haldane, Joseph Needham and Conrad Waddington, with discussions dating from 1936 on the then 'new' subject of molecular biology, its implications for evolutionary theory and the formulation of the Modern Synthesis. Connoisseurs of history will not be surprised by the fact that the title of Popper's lecture was 'A new interpretation of Darwinism'. It was given in the presence of Sir Peter Medawar, Max Perutz and other key figures; it must have shocked his audience.

He proposed a radical interpretation of Darwinism, essentially rejecting the Modern Synthesis, by proposing that organisms themselves are the source of the creative processes in evolution, not random mutations in DNA. Popper suggested Darwinism was not so much wrong, but seriously incomplete. He also stated that biochemistry (and so *a fortiori* physiology) could not be reduced to physics and chemistry.

Many of the points made in the recent special issue of *J Physiol* were therefore made nearly 30 years ago. So why did I and the other 35 authors in the special issue not know this? The answer is that, despite 8 years of patient waiting, the written manuscript was not submitted to the Royal Society before Popper's death in 1994. Worse still, his documents remain archived and closed until 2029.

Hans-Joachim Niemann has, however, worked with the executors to repeal the classification and obtained a copy of Popper's lecture article, which is now published for the first time in English (Nieman, 2014). It should be required reading for anyone interested in the fundamental rethinking of evolutionary biology. Niemann is a lucid and enthusiastic expositor of Popper's lecture and of the ideas that led to it. He shows that these ideas follow on naturally from Popper's conjectures and refutations approach to scientific discovery.

I think that many of the 'new' ideas can already be found in Popper's lecture. He was heard by a large and distinguished audience, so why was he ignored? One possible answer to that question is that Max Perutz was in the audience and he published a serious criticism of the lecture, arguing that Darwin was right (Perutz, 1986). Actually, Popper did not so much argue that Darwin was wrong, as that his theory was incomplete. The central problem for Perutz was the claim that biochemistry could not be reduced to physics and chemistry. He strongly opposed Popper on this point and said so in discussion after the lecture. The reason why Popper did not immediately reply by sending his article to the Royal Society for publication was that he entered into extensive correspondence with Perutz and wanted to conclude the discussion before finally submitting. By then Popper was in the ninth decade of his life. We should not be too surprised that, despite repeated requests from the Royal Society, the lecture was never published.

How did Popper arrive at his radical position? His way in was his clear understanding of a phenomenon known as the Baldwin effect[1]. Organisms can choose new niches for themselves and their descendants. Moving to a new niche can change the course of evolution even with no mutations whatsoever. That choice is a physiological characteristic of the phenotype, not a change in DNA. So how can it change the course of evolution? The answer is surprisingly simple. In a wild population, in which individual genomes are not identical to the combination of alleles in the adventurous organisms, discovering new niches will be favoured. This is an evolution of the genome by combinatorial selection, not selection of new random mutations. It is not surprising that a logician like Popper should have immediately understood the immense significance of this fact. To illustrate his hypothesis, he even invented an imaginary world, in which there was no competition for survival, no 'selfish genes'. The organisms would still evolve. Of course, the world in which such evolution could occur would have to be effectively infinite in size to accommodate all the organisms that have ever lived. However, this was just a thought experiment, which found agreement with the British developmental biologist and geneticist, Conrad Waddington. Why then do selfish gene theorists ignore it? They do so by taking an atomistic gene-centred view. As Popper saw, it is the insistence on just one atomistic approach that is the problem. Physiologists today will readily see Popper's point. It is combinations of genes, or rather combinatorial interactions between large numbers of their products, RNAs and proteins, that are important functionally. Most single genes contribute very little to complex functions, which is why the correlations between genes and complex diseases have been found to be a matter of large numbers of very small effects, still summing up to a small overall fraction of causation. The atomistic view was never going to be of much use in physiology and pathology.

The second way 'in' for Popper was his appreciation of the significance of the discovery of reverse transcription of RNA into DNA[2]. He saw that this drives a cart and horses through the Central Dogma of molecular biology and was deeply suspicious of sophisticated manoeuvrings and redefinitions to protect the dogma from falsification. In his conjectures and refutations view of science, it is better to acknowledge when a strong version of a theory has been refuted. The strong, original version of the Central Dogma was refuted. But he went further than this. He saw that this could be one of the routes through which Lamarckian processes and wholesale reorganisation of genomes could occur. Again, the philosopher in him wanted to see this recognised, not hidden behind a web of clever re-interpretations. He has been completely vindicated. Wholesale genome reorganisation, what Shapiro, in *Evolution: A View from the 21st Century* (Shapiro, 2011), calls natural genetic engineering, has occurred many times in evolutionary history. Like Shapiro, Popper appreciated the significance of the work of Barbara McClintock[3].

With two such fundamental breaks with the standard theory under his belt, what – if anything – was missing in his 1986 lecture?

Actually, quite a lot. As John Maynard Smith also recognised in *Evolutionary Genetics* (1998), where he wrote 'it [Lamarckism] is not so obviously false as is sometimes made out'. The mechanisms known to twentieth century biologists were very few and could be regarded as the rare exceptions that any theory might cope with, by claiming that such processes were not of any great consequence. Popper's strength was his logical foresight. He could, philosophically speaking, smell a consequence from miles away. He took his own refutation theory very seriously indeed, but not in a pernickety way. Reverse transcription, however one looks at it, was a fissure that could grow into a chasm, as it has. The Baldwin effect should be rampant. All organisms, even bacteria, have what he called 'real activity', meaning goal-directed behaviour that distinguishes them from purely physical and chemical processes in nature. This was his fundamental disagreement with Perutz. No wonder he wished to refine his lecture before it was published. Think of a 90-year-old man, each year flashing by, focusing on what he saw as a discovery of great significance. He knew also that the great majority of the scientific establishment was against him. Lamarck had been rubbished, Waddington side-lined, McClintock ignored until the surprise Nobel Prize rescued her great contribution. I believe he was determined to make his lecture unanswerable.

Had he been alive today, just 20 years after his death at the age of 92, he would surely have been delighted with the discoveries that have shown just how wide that fissure has grown. His views are now seen as not simply gene-centred, but that all levels can be the object of natural selection (Okasha, 2006). The rivers of experimental evidence from epigenetics, natural genetic engineering, niche theory, symbiogenesis, and much more have totally changed the landscape of biological theory. The mighty scientific establishment that Popper faced is now a much smaller conservative group of those who still wish to defend the standard story against all comers. My belief is that they can do so only by rearranging goalposts, by redefining the boundaries of what the Modern Synthesis can contain.

Remember too that this is the Popper who wrote *The Open Society and its Enemies*, opposing closed society dogmatism; the Popper who narrowly escaped the holocaust (he included racism as one of the disastrous social consequences of the language of neo-Darwinism, which he realised was largely colourful metaphorical veneer); the Popper who advised us not to hide clear refutations of scientific theory in over-sophisticated manipulations of the goalposts through endless redefinitions. Dogmatism in all its forms, and most particularly in science, was his enemy.

[1] In the 1986 lecture Popper writes: 'My problem is exactly the same as that of my forerunners, such as Baldwin, who felt that the activities ... of individual organisms have played a far more important role in the history of evolution than Darwinists have as a rule admitted.' I suspect he meant 'neo-Darwinists' rather than 'Darwinists'. Darwin admitted the role of organisms and their emotions, and he accepted Lamarckian inheritance.

[2] In a 1973 text reproduced by Niemann, Popper writes, 'There is however a mechanism [he then describes transcription of RNA into DNA]. If this is taken as established it means that it is possible that enzymes exist in all cells which can re-translate RNA into DNA.' Later in the same text he writes, 'It would constitute a break with current dogma.'

[3] Barbara McClintock (1902–1992) was an American geneticist who won the 1983 Nobel Prize in Physiology or Medicine for her discovery of genetic transposition, or the ability of genes to change position on the chromosome (http://profiles.nlm.nih.gov/LL/).

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Great textbooks of physiology

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The first article in this short series (*PN*94, Spring 2014, p. 9) started with the remarks: 'The age of great textbooks of physiology seems to have passed. Those splendid thousand page volumes that used to inform and perhaps intimidate, have – like battleships – disappeared. But actually, we can still learn a lot from these books. In this article, I am discussing just a few of the 'greats' from 40 years ago.' In that article, I revisited Ruch and Patton's *Physiology and Biophysics*. Now I turn to three more examples of Great Textbooks.

General Physiology

Hugh Davson

Hugh Davson (1909–1996) probably knew as much as any one person could know about general physiology or biophysics. His *General Physiology* appeared as a single volume in 1951 and in its final two-volume form in 1970. By then, it had become a standard work and few professional physiologists lacked a copy. It is an extraordinary book. Davson's approach to physiology and his unusually fluent prose style are well shown in the preface to the first edition. He points out that advances in general physiology depended on the recruiting of scientists trained in non-biological subjects (his own training was in chemistry) and noted the difficulties under which those trained only in the biological sciences must labour. His honesty is transparent. How many authors would thank their employers, in his case the Medical Research Council, for having '…silently acquiesced in the theft of so many hours, devoted to this book, which might perhaps have been better employed in original research…'?

How did he write such a book? By spending thousands and eventually tens of thousands of hours, reading and summarising the results of original papers in the library of the Royal Society of Medicine. His approach was straightforward: he read only original papers (he deliberately eschewed reviews and monographs); he collated the results and sources onto filing cards and typed up his findings in the evenings. He set out to read everything relevant to his subject and although he described his approach as 'haphazard', it seems unlikely that any physiologist has ever read more. In addition to this almost unimaginable labour, he ran an excellent research group, established and maintained his position as a leading authority on the physiology of the eye and cerebrospinal fluid and as the doyen of membrane physiology. The range of subjects covered in depth in his book is most impressive. From the mechanics of flagella, DNA, the molecular biology of connective tissue, diffusion processes, electrophysiology, photosynthesis, the gut, the kidney, cardiac muscle – the list is endless. And all in faultless, flowing English.

Davson's *General Physiology* was a unique book. It contains much information of classical importance and anybody who thinks he or she has a new idea in membrane physiology would be well advised to read Davson before applying for a grant. But more valuable perhaps than the scientific information is the opportunity to meet Davson. Nobody will write, and certainly nobody will be paid whilst writing this sort of book again.

Principles of Human Physiology

Ernest Starling

According to Sir Charles Lovatt Evans, Starling dictated much of the first edition of *Principles of Human Physiology (PHP)*. Perhaps the text might have been shortened, but as it stands, it links us immediately with Starling: brilliant, impatient and busy. Starling's pupil Charles Lovatt Evans took over after Starling's death in 1927 and the book changed. More details, references and historical introductions to sections were added. Lovatt Evans wrote (not edited) all the editions up to the 12th in 1956, and then handed over to Hugh Davson and Grace Eggleton who, as editors and contributors, produced two more – the last appearing in 1968. Again, the book changed. No longer a single author work, it now comprised a series of eight 'books' or monographs, each contributed by an expert. It is the final, 14th edition which is considered here.

Even in 1968, *PHP* looked more like a reference book than a textbook for students. E M Killick, in reviewing the 12th edition, commented that the book had 'one great defect as a textbook, namely, that medical students find it extremely difficult to read.' A damning comment, but softened by her praise for the work as a reference book for teachers of physiology.

The 14th edition contains contributions of outstanding quality. M de Burgh Daly's 500 or so pages on blood, the circulatory and respiratory systems (with contributions by Davson), and D H Smyth's account of the gut are excellent pieces of work. Davson contributed extensively: 558 pages on the CNS and special senses in addition to the Introduction and sections on tissue fluids and the CSF. Davson told me that he had written the section on the CNS after having been let down by a distinguished neuro-physiologist. Although the CNS was not Davson's special area of interest, he excelled in a fluent and exhaustive style, dealing with the anatomy as well as the physiology.

Rushton's chapter, 'Nerve Fibres', is still worth reading today. He wrote in a classical style introducing striking analogies 'Like ships anchored to their buoys, the K^+ ions cannot drift away but all swing on their moorings in one direction with the set of the tide.'

But as sales dropped, Davson deplored the decision to drop the book and responded in style with a new book that he wrote with Malcolm Segal: *An Introduction to Physiology*. This ran to five volumes, the first two providing an admirable introduction to the subject, the latter three providing more detail along the lines of *PHP*. Volume 3 is devoted to the control of the major systems. Davson's preface, in which he distinguishes sharply between an Introduction and a Synopsis, is worth reading. But even at five volumes the book remained incomplete and no further editions have appeared.

Principles of Human Physiology was a great reference book. In its time, there was hardly a fact likely to be needed by a student of physiology that could not be found between its covers. It remains a splendid account of classical physiology and contains valuable information.

Medical Physiology

Vernon B Mountcastle

'Mountcastle', as the book was usually known, was the largest of the great textbooks of physiology of the 1970s period. Two large volumes, 1858 pages plus an index – a long book – *Medical Physiology*, like the other books considered in this series, had a long history. It appeared in 1918 and was edited for many years by Philip Bard from Johns Hopkins University. The 14th and final edition appeared in 1980: 1999 pages plus 72 pages of index. One volume was devoted to the nervous system (and muscle); the other to the remainder of the subject. Rather confusingly, the order of the volumes was reversed between the 12th and 14th editions.

The approach taken by all contributors involved a great deal of detail. Illustrations were adequate but not prolific and the impression received by the beginner was one of long passages of rather solid text. This was off-putting to some; to others the depth of treatment was rewarding and the standard of the work was clearly a long way beyond that of 'ordinary' textbooks of medical physiology.

The series of chapters, which seemed to be particularly good were those on sensation contributed by Mountcastle himself. His work on the organisation of the cerebral cortex in columns of neurones was well known of course and his expertise glowed in these chapters. But not all the CNS chapters were up to date, indeed several had not been revised at all from the earlier edition of the book.

'Mountcastle' was the largest textbook of physiology available in the 1960s. It provided a detailed account of those aspects of physiology useful to medical students and to doctors. But it was long! It lacked the punch of Ruch and Patton's *Physiology and Biophysics* and the 1980 edition was the last. Students no longer read such long books: the loss is theirs.

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An affiliate's view on networking and mentoring

Fiona Hatch

University of Surrey, UK

Fiona at the Registration Desk at Physiology 2014

I turn up at the registration desk for Physiology 2012 in Edinburgh and I escape into my delegation bag and mobile phone as a distraction from the disturbing truth – I do not know anyone. This is the same for many other affiliates year on year. Though two years on, after diving into the society quiz night and an awkward piano performance at 'Physoc's Got Talent' on that very same first intimidating day of the conference, the thought, 'I do not know anyone' could not be further from the truth.

Currently as Affiliate Representative to Council of The Physiological Society and a member of the Policy and Education and Outreach Committees, I know both Physoc staff and countless members and affiliates. In this time I have presented seven scientific posters, given one oral presentation, won two poster prizes and played a role in the policymaking and physiology education and outreach agendas. But this is not about me blowing my own trumpet; instead I'm writing to explain as an affiliate that to start off with, everyone is in the same boat and it is very daunting trying to keep that boat afloat.

As part of the Education and Outreach Committee I took upon myself (with the help of Keith Siew) to revamp the Mentoring scheme and help integrate affiliates into The Society. The aim was to provide interested affiliates with advice on how to get the most out of a conference and the benefits of having a mentor. The revamp consisted of two parts; firstly the Early Career Social (ECS) which at P14 was held in the Albert pub in Westminster. With over 50 affiliate attendees it was a successful meet and greet social. Secondly I organised the Networking and Mentoring workshop – a pilot workshop that I hope to build upon in the future. This involved a panel of mentors – Sue Wray (University of Liverpool), Chris Fry (University of Bristol), Lucy Donaldson (University of Nottingham) and Jeremy Ward (King's College London). All of them are successful physiologists, with experience in being a mentee and a mentor, and were able to provide us with a lively discussion and overall top tips. Alongside the mentor panel, were two mentees, Keith Siew (University of Cambridge), who is completing his PhD thesis currently, and me, coming to the end of my first post-doctorate position.

Types of mentoring

Mentoring The mentor is typically senior and may or may not be within your field but regardless, they will still have the experience and support you require. Ensure your expectations of a mentor are realistic. Keep in mind what your aims are; in this way a mentor could help guide you through your chosen career path.

Peer Mentoring You'll gain different perspectives/experience from a peer along with it being less intimidating for you to bring your problems to them, they sometimes offer frank advice that a senior mentor might not. Furthermore this is mutually beneficial to both parties as its reciprocal nature allows one to be both mentor and mentee.

It is false to think that once you have acquired said mentor (see Box 1), life suddenly becomes easier. 'Mentors are not knights on white chargers, they are personal trainers who show you the route, act as a guide, but you have to do the work', said Lucy Donaldson. This is a similar ethos to networking; relying on others to introduce you to their contacts is the best and simplest route, but sometimes this is just not possible, and in some cases you have to just bite the bullet and throw yourself into the crowd. Conferences are one of the best places to network, be it to find your next collaboration, future employer or potential mentor. It is a mistake to believe that the communication of your poster or oral presentation is the only benefit; remember to take advantage of the social events and talk to new people. Contacts are always important for career progression through academia; therefore attend as many presentations as possible, broaden your knowledge and push yourself to ask questions. Set yourself goals for the conference, mark abstracts and talks that are of key interest ahead of time and make a note of the people you may want to approach – a welcome reception or dinner event is perfect for this. This becomes significantly easier with practice, but to start

Networking in action at Physiology 2014

you off I've provided you some top tips, as discussed and agreed upon by our panel of mentors and mentees (see Box 2).

On the outside, you would assume I'm an outgoing people's person, willing to engage and debate topics on a peer level with prominent scientists on a council of trustees and not be easily intimidated. But this is far from the truth; this 'personality' is a skill that I have developed over time, through all the shy and awkward encounters, through the 'out of my league' conversations and seemingly intimidating physiologists. Portraying self-confidence is a mask that many people use, but after a while, it will be simple and easy to put on; then before you know it, everyone will believe it's your natural personality and you're a gifted networker. Furthermore I would like to debunk the pedestal phenomenon where senior, principal investigators are unapproachable 'god-like' physiologists. It is important to remember they were once in the same situation as you; the majority of physiologists are amicable people and many have egos regarding their own work and would love to have an intellectual discussion with you. To quote Sue Wray, 'You have to learn to force yourself to flick that switch that turns you into Ms or Mr Congeniality. Go into that room, smile and start a conversation. Usually the cringe-making horror subsides and you realise you are simply having a conversation and before you know it, you could be enjoying it, not just surviving it.'

Sue also recommends getting on Google and looking at hints and tips for 'networking for people who hate to network'. So next time, do not hesitate in approaching someone, plaster a smile on your face, proffer a solid hand shake and introduce yourself – the first time is always the hardest.

Occasionally the link between networking and mentoring is unclear. You do not require a lasso and a contract detailing your relationship with your mentor, ensuring they're tied to you in every way possible. Although I have previously been allocated a mentor, I have been supported more by those around me that have not been rubber stamped as my 'mentor'. They are interviewers I've met after a failed post-doc interview, Physoc Committee Chairs who have listened to my problems and proffered wisdom and encouragement, and fellow PhDs and post-docs that have echoed my thoughts and provided frank advice. This would not be possible without networking: by removing my head from my delegate bag, putting my phone away and walking up to a fellow physiologist.

But regardless of any achievements, I continue to have the same problems as every other affiliate: where will my next job be? who has grants/funding? and the pressures, problems and writer's block associated with papers. Nevertheless, I am fortunate enough to have mentor figures I can go to for advice and support, and ultimately this is what helps me keep my boat afloat.

Top tips for conferences

- Look at the programme carefully in advance. Often there are interesting sessions on allied subjects that you may miss. If there is an interesting session or lecture maybe spend a short time in advance looking at some background to the area or the speaker
- Ask questions – don't leave it to the person next to you, do it yourself. There's no such thing as a silly question, only the one that you didn't ask, and therefore never got answered.
- Do go and talk to the speaker afterwards. Ask about their work, talk about your work when relevant, but don't turn it into a sales pitch. Explain why you are interested in speaking to them and how their insight might help you, or broaden your knowledge.
- However shy you are, you have to make yourself talk to people. At a poster, in the lunch queue, at meal times. Wherever you go and whatever you do, you will have to be able to speak to people with confidence. Generally most people, no matter how senior, are pleased to spend a few minutes to speak with you about a particular area that you wish clarified or explained.
- If you're at a meeting with your friends – leave them and go find new people to talk to. Have in mind to make new colleagues and acquaintances – extend your group. You never know who those new people also might know.
- Try not to drink too much – at the social events always be alert and ready to network.
- Don't start a conversation with a 'what's in it for me?' mentality. Instead of thinking someone can help you out, try reaching out with curiosity. Contact interesting people and see where the relationship goes down the line.
- Once you obtain an email address to a key contact, follow it up within a fortnight of the meeting regarding your discussion at the conference.
- Many physiologists know each other personally. This is useful when introducing yourself to a new senior contact; sharing who you work with (now or previously) may be your biggest opener.

Physiology to pedagogy

Nicholas Freestone

University of Kingston, UK

Receiving 'Most Helpful Male Lecturer' award from the Kingston university pharmacy students' association in 2012

Background context

For UK physiologists working as lecturers in universities, research in that discipline is probably what defines them in terms of their professional roles and expertise. However, we are living in changing times and along with being skilled at the practice of our discipline many of us must also transmit physiological knowledge and expertise to our students, who will be the next generation of physiologists, as well as to the public who need a better understanding of physiology. Life as a physiology academic has shifted from one rooted purely in the discipline to one which must engage with the pedagogical aspects of that discipline for the benefit of our student learners. This dispositional shift experienced by many of us will only be accentuated in the future as the cap on student numbers is lifted by the government in 2015. How is the physiology academic to respond to these pressures and drivers at a personal level as well as at an institutional level where increasing student numbers on expensive laboratory-based courses will be the subject of particular stresses and strains? The massification of the HE system invariably means that time available for research is also severely constrained so we may have to concentrate on the learning and teaching and administrative aspects of our roles, whether we want to or not.

Up to the present, the state has allowed large increases in the number of students feeding through the university system with no corresponding increase in state funding to manage these greater numbers of students. This may be thought to be a serious detractor of teaching quality. It has, however, at least had the effect of drawing attention to the pedagogical responses needed to cope with the new stresses imposed upon the HE system. Since the Dearing Report (1997), the professionalisation of university teaching has been a much cited aspiration in the UK HE sector.

'Effective teaching and learning is essential if we are to promote excellence and opportunity in higher education. High quality teaching must be recognised *and rewarded*, and best practice shared' (my italics).

The above quote was contained in the UK Government's 2003 White Paper *The Future of Higher Education*. However, it is not readily apparent that teaching in the university sector has been rewarded in the way envisaged. More recently Willett's report for the Social Market Foundation (Robbins revisited: Bigger and Better Higher Education, 2013) explicitly places the student in the role of consumer of goods and services provided by the HE system. All of the costs of a degree are now placed onto the prospective student. In this context, emphasis on high 'quality' teaching rather than discipline-specific research would seem to be even more of an imperative for UK universities. In particular Willetts wanted to 'strengthen the incentives to focus on teaching' as he deemed that the pendulum had swung too far in favour of rewarding excellence in research (Willetts, 2013).

Even now, the role of learning and teaching in UK universities has not had the attention that it deserves. Many of us currently teaching physiology were probably not formally qualified to teach when we entered academic life. In my case, my research experience of spending days alone in a darkened room staring at fluorescently labelled cardiac cells down a microscope probably made me poorly suited to teach Introductory Physiology to large cohorts of eager first year undergraduates. I am sure this is similar to the experience of many other colleagues. However, the lifting of the cap on student numbers and the introduction of student fees has been driven, in part, to elevate the role of learning and teaching at universities and to make student satisfaction with their educational provision key determinants of university performance measures.

In responding to this challenge the HE sector has, so far, paid lip service to the concept of the professionalisation of university teaching (Cashmore *et al.* 2013). It is still undoubtedly true that career progression for colleagues across the sector is more straightforward when it is concentrated on the research arm of their practice. Career progression for those colleagues focusing on the learning and teaching aspects of their practice is not so simple. Thus it remains the case that there are very few pedagogical professors in the STEM subjects in UK universities and even fewer in the discipline of physiology.

This may be due to the fact that, as the Higher Education Quality Council stated, 'at least part of [the] problem might be that universities had not adequately addressed the issue of what makes up quality in teaching'. Therefore, the reluctance of UK universities to promote academics through their teaching ability alone may reside in the fact that objective criteria to compare the 'excellence' of different academics' teaching are absent. This fact contrasts markedly with the promotion path for research-orientated academics where objective criteria for progression are explicit, transparent and adhered to (publication outputs, grants received, PhD completions, etc.). This places the learning and teaching specialist at a significant disadvantage for advancement within the UK HE sector.

So we have a context whereby we have in the recent past seen a massive expansion in student numbers, a future where this expansion may further increase and a government intent on rebalancing the role of teaching relative to research in part by making student satisfaction one of universities' key performance indicators. What mechanisms are there in place that might help lecturers to manage these complex and multi-faceted challenges?

Academics' possible response

Most universities now require new academics to enrol on postgraduate certificate in education-type courses. These tend to give rather generic instruction in the fundamentals of learning and teaching and are received with varying degrees of enthusiasm by the participants. More recently many institutions have aligned elements of their career progression criteria to the revised United Kingdom Professional Standards Framework (UKPSF) launched by the Higher Education Academy (HEA) in 2011. This framework seeks to benchmark 'success within HE teaching and learning support' (HEA, 2014). The possibility of progression in the university system by evidencing strengths in learning and teaching underpinned by the UKPSF has encouraged many colleagues to seek Higher Education Academy (HEA) recognition linked to the various dimensions of the UKPSF. To aid colleagues in this process, all of the HEA events in the coming academic year (15 in total nationally) will be explicitly mapped to the UKPSF.

At different stages of one's career, one can apply to become an Associate Fellow, Fellow, Senior Fellow or Principal Fellow of the HEA. Whilst this scheme has been promoted by the HEA, many individual institutions are also now able to award their own fellowships accredited by the HEA. There is also the facility to obtain recognition online (by logging in to the MyAcademy section of the HEA website) making the application process quicker and easier. One would then be able to demonstrate Continuing Professional Development (CPD) by participating in events, developing learning tools or undertaking pedagogical research. It may be the case in the future that, by benchmarking one's role against the UKPSF and HEA Fellowships, one may more easily delineate a career path characterised by an emphasis on the pedagogy of physiology.

My own story

My own career progression in a post-1992, multi-faculty civic university which wholeheartedly endorses a Widening Participation ethos, has indeed been helped rather than hindered by a focus on the learning and teaching aspects of my role (this might be expected given that it is not a research-intensive university but even here it has been the case in the past that promotion was more easily gained through a focus on research). Upon taking up my first academic position I was quickly thrust into the development of a new degree programme important for the sustainable future of my School. It was necessary therefore for my immediate focus to be on the development and subsequent administration of a coherent new learning programme. This, of course, severely restricted my opportunities to develop a laboratory-based research programme in the crucial early years of my academic tenure.

Teaching in the laboratory

However, despite the frustrations that this situation caused, it gradually dawned on me that all of the basic elements of a research area were readily available. I had become increasingly interested, due to my prolonged and close contact with undergraduate students, in how they learned and negotiated their way through their degree programmes. Getting to know my learners as individuals opened up a vast array of interesting personal circumstances, experiences and learning styles that I found increasingly fascinating. How could I develop this interest in the process of learning into a fruitful area of research?

Here, again I was very fortunate to, almost accidentally, come into contact with the Biosciences special interest group of the HEA. This provided a very supportive, collegial and collaborative environment in which to gain exposure to, and experience of, the application of qualitative social science research methods in pursuit of knowledge about the nature of learning in our UK HE context. I quickly came to realise that such research was not so dissimilar from our quantitative laboratory-based physiological research, i.e. find an interesting research question, use the most appropriate method to investigate that question, obtain data, analyse the data and then disseminate it at conferences and/or in papers (here The Physiological Society deserves a special mention for continuing to sponsor an Education and Teaching Theme at its annual Main Meeting).

Apart from career progression and promotion (which as pointed out previously are not necessarily rewards for engagement with pedagogy) there are many prizes awarded for teaching excellence that may motivate the putative pedagogue. As a prime example, The Physiological Society itself offers not only the annual Otto Hutter Physiology Teaching Prize (the exceptional recipient in 2013 being Dr Dave Lewis from the University of Leeds) but also the David Jordan Teaching Grants to enable those who focus on learning and teaching to undertake a pedagogical research project. Similarly, the HEA, in conjunction with the Society of Biology, has offered the HE Bioscience Teacher of the Year Award (of which I am this year's unworthy recipient!). There are equivalent prizes and awards offered by many of the other STEM disciplines and all seek to elevate the role of learning and teaching in UK universities. It has to be pointed out, however, that the research in this area is ambivalent on the awarding of prizes as a driver of general improvements in teaching and subsequent quantifiable gains in student learning.

Nevertheless, it is probably likely that given our current circumstances, universities will be forced to more explicitly address the learning needs of their students. This would best be done by rewarding academics' engagement with their learners and the processes of learning. I believe, therefore, that it is incumbent upon us academics to grapple with the pedagogical elements of our roles to ensure that, even in these uncertain times, student learning is placed at the forefront of our academic practice.

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ETRIS: facilitating research and training in *in vivo* physiology

Dave Lewis

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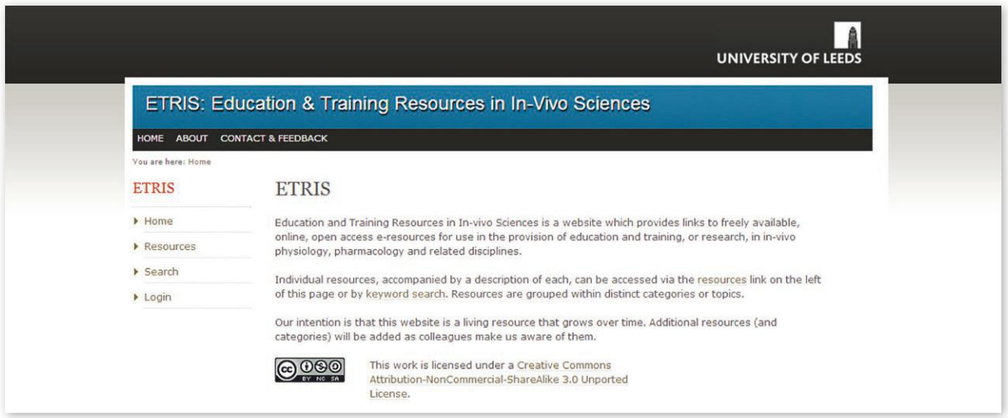
The transposition of EU Directive 2010/63/EU in UK law has introduced new training and competency requirements for scientists working under the Animals (Scientific Procedures) Act 1986. Both the Directive and the amended Act explicitly state that staff must be 'adequately educated and trained' and 'that they shall be supervised in the performance of their task until they have demonstrated the requisite competence'. In addition to initial Home Office accredited modular training, there is now also a requirement, throughout a researcher's career, for them to receive continued on-the-job training, to participate in other continuous professional development activities, and to have a reassessments of their competencies at regular intervals. 'Training for the acquisition, maintenance or improvement of vocational skills' is a permissible purpose under the amended Act and therefore all researchers (not just practising microvascular surgeons) can now use research animals in their training, as well as in the development and maintenance of their technical competencies.

However, the use of animals for training is contentious. They should only be used, if absolutely necessary, and only during the final stages of training. For example, after the observation of similar studies, viewing or utilising electronic resources, and practising the setting of experimental preparations using cadavers. Electronic resources are increasingly being used in the early stages of this process to supplement hands-on experience. Whilst many excellent e-resources have been developed, significant numbers are locked behind the websites of institutions, commercial or professional organisations, only available to members or subscribers. Those that are freely available are often unknown to the community.

In response to this problem, ETRIS (Educational and Training Resources in *in vivo* Sciences, **www.etris.leeds.ac.uk**) was developed. ETRIS is a website which provides direct links to free, open access, or open educational e-resources which deliver training or facilitate research in *in vivo* physiology and pharmacology. In addition to a direct web link to individual resources, each is accompanied by a descriptive paragraph which outlines what is in the resource, its provenance, copyright or access restrictions and suggested usage or audience. All resources are vetted to ensure compliance with the Animals (Scientific Procedures) Act and best practice in the 3Rs. Resources are grouped into 13 categories spanning the entire spectrum of resources required by practising *in vivo* scientists including animal welfare and husbandry, ethics and the 3Rs, experimental and statistical design, and surgical procedures. ETRIS is free to use, and no log-in or registration is required. Individual resources can be located using the search function or clicking on a resource category.

The plan is for ETRIS to be a living repository of resources, which grows and expands over time. However, this will only happen with the help of the community. Therefore if you have any e-learning or training resources, including, but not restricted to, videos, podcasts, guidance notes, software or educational protocols that you are willing to share or know of any relevant resources on open access websites, please contact Dave Lewis at **3Rs@leeds.ac.uk**. Resources do not have to fall within existing categories; resources in other areas not currently covered are also required. Likewise, please use ETRIS; share the site with your colleagues, link to it from your institutional or company Biomedical Services or Home Office websites. Your feedback on the site or individual resources would also be appreciated.

ETRIS was developed through the award of a University of Leeds Teaching Fellowship to Dave Lewis. The support of the University for this project is gratefully acknowledged.



Do you know about the Benevolent Fund?

Thelma Lovick

Benevolent Fund Chair

The Benevolent Fund of The Physiological Society (the Ben Fund) is a charity within The Society, which was established by Trust Deed in 1976 'for the purpose of assisting Members of The Physiological Society ('The Society') and staff and former staff (who by the nature of their employment can be considered to have contributed to the advancement of physiology) employed at teaching, research and industrial establishments who are in necessitous circumstances and their dependants'.

What does this dry legal statement mean in real life?

What it means is that there is a relatively small pot of money that can be called on to help anyone associated with Physiology. The beauty of the Fund is its simplicity and rapid response.

How does the Fund work?

The Ben Fund works within a formal framework but in an informal rapid response mode. There is no formal application form. Applicants simply email one of the trustees or The Society's office and make a case for support. The request is then emailed to the trustees who confer, again usually by email. A decision is normally reached within a few days.

Who can apply?

Anyone can apply but applications usually come from members of The Society who have identified a needy cause. This is not necessarily another Society member; the only criterion is that they have contributed to the advancement of physiology in its broadest sense. So this might be another scientist or a member of their family, or a member of technical or domestic support staff in your institution who contributes to the advancement of physiology in an indirect way. We rely on members to identify a deserving case and alert us.

Who decides on awards?

There is a small committee of elected trustees comprising the Chair, three Society members and two *ex officio* members (the Society's President and Treasurer). The committee meets formally once a year; in the past this has been immediately before the AGM, usually to coincide with the main summer meeting. However, most business throughout the year is conducted by email. All applications are treated in confidence and considered on a case-by-case basis.

Who administers the Fund?

The Ben Fund is a separate Trust from The Physiological Society. However, it is administered by The Society's officers. Our expenses are therefore very low.

Where does the money come from?

The Fund relies from donations from Society members. Typically this is in the form of one- off or regular donations. As we are a charity you can Gift Aid your donation, which increases its value to the Fund by 25%, as we can claim the tax back. A small amount of money is also generated by events like raffles. Retired and Honorary Members of The Society, who no longer have to pay a membership fee, sometimes donate their subscription to the Fund, which is much appreciated.

How much money is there?

The Ben Fund is a very small charity, so awards are relatively modest. In recent years grants have ranged from £200 to £2000. The beauty of the Fund is that we can respond very quickly. In an emergency, even a relatively small sum can make a significant difference to people's lives.

Some examples of awards:

Health and carer support including assistance towards specialist wheelchairs, home adaptations, mobility equipment and respite care (including welfare breaks).

Short-term financial assistance in the form of grants and donations when you are facing exceptional financial difficulties including funeral arrangements, medical treatment, grants for re-training and childcare arrangements.

What is excluded?

We cannot fund applications for travel to meetings, student fees or stipends, seminars or meetings. This is outside the remit of the Trust and there simply isn't enough money, however worthy the cause.

Find further information about the Ben Fund and make a donation on the Fund's website **www.physoc.org/benfund**

Obituary:

Alex Livingston 1930 – 2014

Alex Livingston BSc BVetMed PhD FRCVS Dip ECVPT, a prominent figure in veterinary medicine and science, died of a heart attack after a short illness in June 2014, 10 days short of his 74th birthday.

Alex was recognised for his leadership and research advances in the areas of animal pain, animal welfare and pharmacology of analgesics. He was awarded the Merial Grand Prize for Outstanding Research in Animal Pain in 2001.

Alex grew up in Luton during the Second World War. Here he spent much time with his Granddad who had a collection of shacks where he kept ferrets, dogs, chickens and other animals until he sold them. This experience no doubt led Alex to a love of animals and a desire to study veterinary medicine at university.

He gained a place at the Royal College of Veterinary Medicine in the University of London, where he intercalated a BSc in Physiology in 1962. He continued his course to complete a veterinary medical degree, B Vet Med, and MRCVS in 1964. He then moved to Bristol to study for a PhD with Dr K Lederis in CNS pharmacology, which he completed in 1968. His later research focused on the action of chemical messengers in the brain areas involved in pain perception and how drugs that can alter these actions affect the way animals respond to pain. His concern for the welfare of animals made him aware of how little was understood about an animal's behaviour associated with pain, which he felt was different to humans.

Alex became lecturer, then senior lecturer and then in 1991 acting head of Pharmacology in Bristol. In 1992 he moved to Canada to take up the position of Dean at the Western College of Veterinary Medicine at the University of Saskatchewan making an important contribution to training of students in veterinary medicine and to their position in Canadian society. He retired from the deanship in 2002 and took up a faculty position until finally retiring in 2007. He had a distinguished career becoming a Fellow of the Royal College of Veterinary Surgeons (FRCVS) in 1993 and Diplomat of the European College of Veterinary Pharmacology and Toxicology in 1999. Throughout his deanship Alex was still involved with graduate research, teaching and mentoring of clinical residents. Alex was also active in the scientific community as board member on the Canadian Council for Animal Care and Editor-in-Chief for *Research in Veterinary Science*. During his career he supervised 15 PhD students and contributed to scientific knowledge with over 100 publications in internationally recognized peer-reviewed journals, and over 20 book chapters. Alex's passion was scientific research for the benefit of animals, but he still managed to run a small farm with a herd of Charolais–Hereford crossbreed cows.

In his younger days Alex was a keen rock climber, exploring cliffs throughout the UK but particularly active on the limestone of Clifton and Cheddar Gorge as well as the sea cliffs of Cornwall.

Alex will be remembered forever for his sense of humour, his love for his family and for his animals. He was a great story teller. He took great pride in his family and all the students he taught and mentored over the years. His later years were spent continuing his academic research, attending auctions and acquiring antiques. He is survived by his wife of 38 years, Sue, and sons Alex, Andy, Ian, daughter Kate, and grandchildren Ellie, Stephanie and Adam.

John H Coote

Professor Emeritus
School of Clinical and Experimental Medicine
University of Birmingham, UK

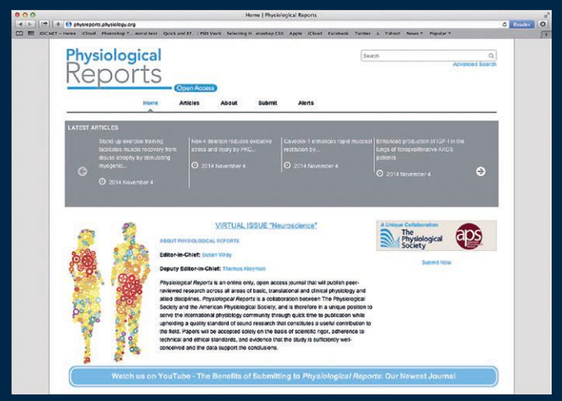
Notices and full obituaries can be found on The Society website at ***www.physoc.org/obituary-notices***

Have you got an ORCID ID?

An ORCID ID provides you with a persistent digital identifier that distinguishes you from every other researcher and, through integration in key research workflows such as manuscript and grant submission, supports automated linkages between you and your professional activities, ensuring that your work is recognised.

Authors can now provide their ORCID IDs with their submissions to The Society's (and many other) journals and although this is not compulsory, we would encourage you to do so. ORCID is an open, non-profit, community-based effort to provide a registry of unique researcher identifiers and a transparent method of linking research activities and outputs to these identifiers. For more information or to register for an ID go to **http://orcid.org/about**

Physiological Reports

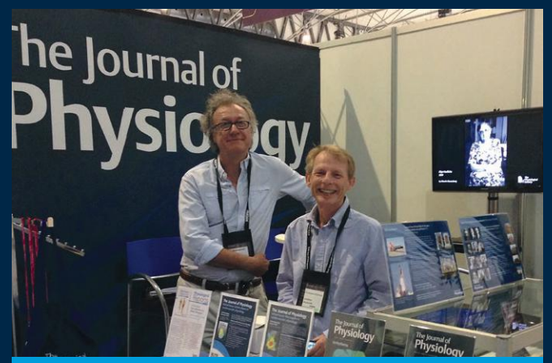


Virtual Issues

To coincide with **Obesity: A Physiological Perspective**, held in Newcastle on 10–12 September, *Physiological Reports* produced a virtual issue entitled **New Insights in Energy: Homeostasis, Fat and Obesity**. Associate Editors Julian Davis and Gareth Leng selected articles on this subject published in the last year. There was another virtual issue to coincide with the annual meeting of the Society for Neuroscience in November, with articles selected by Gareth Leng. These displayed the range of Neuroscience topics that *Physiological Reports* has attracted, and also reflected those aspects that give the journal a distinctive identity and rationale, namely negative findings, the application of computational modelling, and making maximally accessible original data of potential secondary use.

The Journal of Physiology

David Paterson made Honorary Fellow of RSNZ



Editor-in-Chief David Paterson and Production Manager Jonathan Goodchild, at the ESC Congress.

We are delighted to announce that Professor David Paterson, Editor-in-Chief of *The Journal of Physiology*, has been elected as an Honorary Fellow of the Royal Society of New Zealand (RSNZ).

The Journal at the ESC Congress

Barcelona, host to this year's European Society of Cardiology Congress, greeted us with warm sunshine and a variety of exciting comestibles. Despite the laid back 'mañana' attitude that we often associate with the Spanish, the meeting at Fira Gran Via was well organised and went very smoothly.

In 2013, we attended the AHA Scientific Sessions meeting, but this year we chose to target the ESC meeting as we felt that the programme was more suited to our focus on basic research. This was the first time in recent years that we had attended a major international meeting in Europe and the demographic of the attendees was strikingly different to that of the US meetings that usually form our conference schedule. There were very few people from North America, but many from South America, Eastern Europe and Asia. Of the 300 or so people that we spoke to, over 75 countries were represented – a pretty impressive statistic!

Although aware that we were targeting a new audience, we were still surprised that many people had not heard of *The Journal of Physiology*. We were therefore pleased to be able to educate them on the long and interesting history of *The Journal* and The Society, and highlight some of the key papers in the field of cardiovascular physiology that had been published in *The Journal*. We had virtual issues highlighting both classic and new cardiovascular papers and historical information listing our Nobel Prize-winning authors and seminal works. The 2013 special issue dedicated to arrhythmia was also promoted and was very well-received.

We usually expect to be asked about submission requirements, policies, cost and speed of publication, but the audience here were far more interested in reading our content. This is probably because many of the delegates were clinicians who need to keep up-to-date with advances in cardiovascular research, but are unlikely to look to us as a potential publishing option. Despite this, we are looking forward to building up a relationship with this new community of readers in the coming years.

The Journal at Neuroscience 2014

As ever, *The Journal of Physiology* had a stand at the Society for Neuroscience's annual meeting, this year held in Washington, DC. It was another great opportunity to engage with our growing pool of neuroscience authors. *The Journal of Physiology* compiled a Neuroscience virtual issue, which featured recently published, high-quality research papers and review articles. The selected papers demonstrated the broad scope of our neuroscience content, ranging from research at a cellular and molecular level, to cognitive and behavioural work, as well as studies on the neurobiology of disease.

New Editors for *The Journal* from January 2015

We are very pleased to announce that the following people will be joining the Editorial Board as Reviewing Editors in January 2015:

- David J Adams (RMIT University, Australia) – neuroscience and membrane physiology.
- Greg Funk (University of Alberta, Canada) and Frank L. Powell (UCSD, USA) – respiration.
- Anne McArdle (University of Liverpool, UK), Troy Hornberger (University of Wisconsin – Madison, USA) and Bettina Mittendorfer (Washington University in St Louis, USA) - exercise physiology and muscle.

Experimental Physiology

Connections

Experimental Physiology has been making Connections by identifying a sequence of three related articles (each one citing the next). The author of the middle article outlines their article's principal novel findings and traces how they were influenced by the previous article and how they have contributed to the following article. The author speculates on where that might lead in future research and places the article in a wider context in a style that makes the subject accessible to a broader readership.

You can find more information at **http://ep.physoc.org/cgi/collection/connections**

New *EP* Editor

Professor L Ashley Blackshaw from Queen Mary University of London joins EP as a new editor.

His research focuses on gastrointestinal sensory mechanisms in a range of disease indications including pain, obesity and reflux disease.

GL Brown Lecture 2014

The 2014 GL Brown Lecture by David Eisner **Calcium in the heart: from physiology to disease** has been published (October issue) and is also available on Youtube: **https://www.youtube.com/watch?v=VXSJkq5Dk8o**

Ageing & Degeneration:
A Physiological Perspective

10–12 April 2015
Royal College of Physicians
Edinburgh, UK

www.physoc.org/ageingtopic

The Physiological Society
2015: Understanding Ageing