PN
Physiology
News

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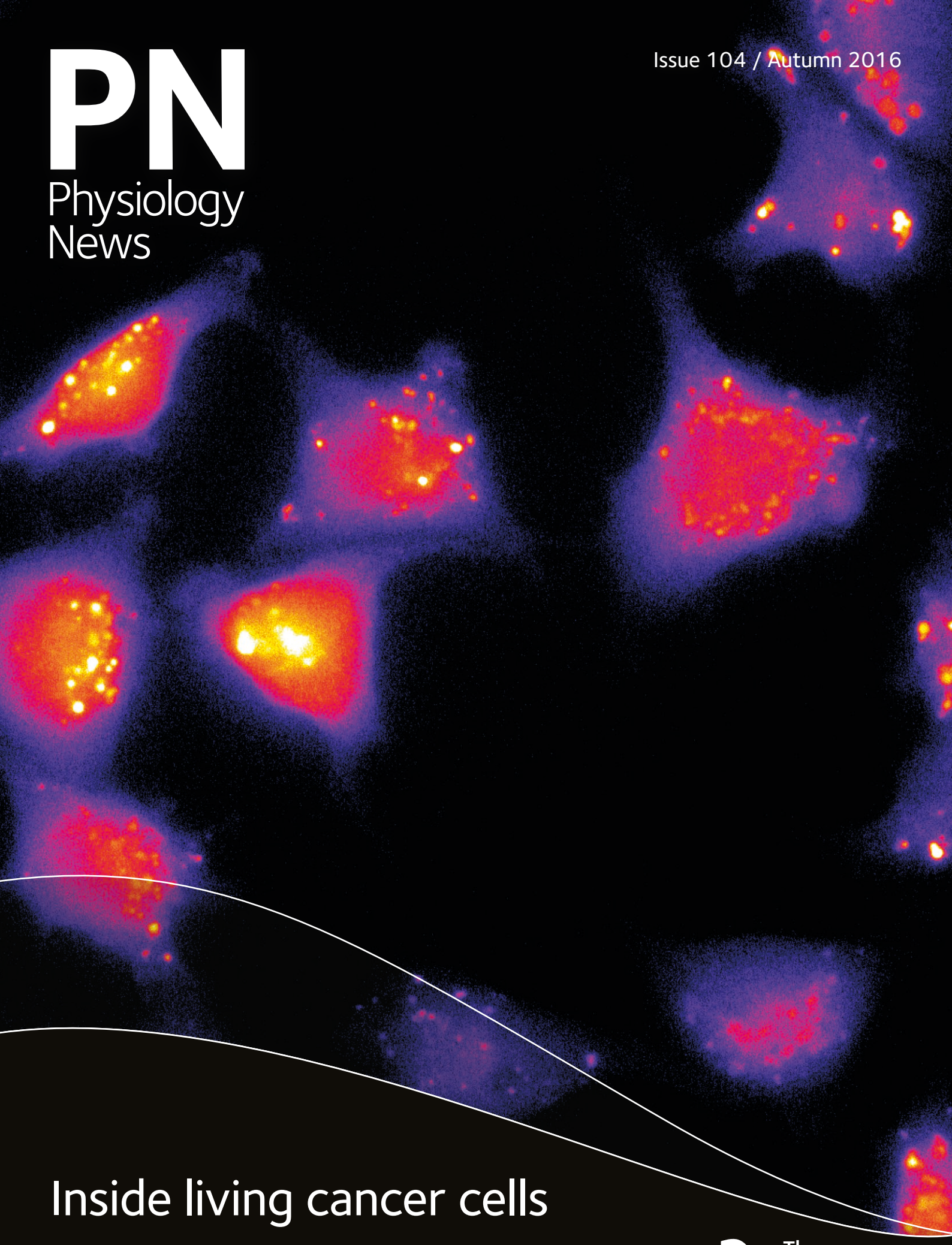

Inside living cancer cells

Research advances through bioimaging

The Physiological Society

H³ Symposium

Gene Editing and Gene Regulation (with CRISPR)

Tuesday 15 November 2016
Hodgkin Huxley House, 30 Farringdon Lane,
London EC1R 3AW, UK

Organised by
Patrick Harrison, University College Cork, Ireland
Stephen Hart, University College London, UK

www.physoc.org/crispr

The programme will include talks on CRISPR, but also showing the utility of techniques such as ZFNs and Talens.

As well as editing, the use of these techniques to regulate gene expression will be explored both in the context of studying normal physiology and the mechanisms of disease. The use of the techniques in engineering cells and animals will be explored, as will techniques to deliver edited reagents and edited cells *in vivo*.

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**

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Welcome to the Autumn 2016 edition of *Physiology News*

Introduction

News in brief

News in depth

Meetings & events

Features

Membership

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Cover image: Imaging glycogen storage in ovarian cancer cells. Tim Witney, UCL






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Karen Doyle

Lecturer, Department of Physiology, NUI Galway

In this edition of *Physiology News*, we have a special feature focusing on research advances through bioimaging, particularly in the area of cancer, with contributions from some of the speakers at The Physiological Society's topic meeting, Advances in Bioimaging, in University of Warwick in August. Tim Witney, one of the organisers of the meeting, explains his groups interest in developing new imaging agents to study cancer and the molecular and biochemical markers that could enable prediction of drug resistance, facilitating improved targeted therapeutics for cancer sufferers. One of Tim's images graces the front cover of this issue. Adam Shuhendler uses activatable molecular imaging nanoprobes, including reactive oxygen species-activated and caspase-3-activated probes that may lead to earlier detection of disease and enable earlier prediction of the therapeutic effect of cancer treatments in patients. Kurt Anderson, talks of the development of newer, better, fluorescent biosensors that can be used to detect disease-related conformational changes in proteins *in vivo* through fluorescence resonance energy transfer (FRET). Recent developments have enabled more extensive use of FRET-based biosensors in pre-clinical cancer models, enabling characterisation of drug response in tumours.

We have an article from Tilli Tansey describing the life and career of Henry Newell Martin - a very celebrated experimental biologist, founder member of The Physiological Society and a champion of the fledgling *Journal of Physiology* during his short life. Additionally in this issue, in continuum with the last issue, we have an insight into the postdoctoral experiences in Cambridge of Mordecai Blaustein. This engaging article reminisces about the seminal experiments that unravelled the existence of the sodium-calcium exchanger (NCX) in the 1960s. It exudes the enthusiasm and excitement of discovery, amusing insights and tales of friendship with mentors and contemporaries in a time of electrophysiology breakthrough that has had such huge impact on physiology generally.

In this bumper packed issue, we also get insight into questions such as what a space physiologist does (Julia Attias), and if there really are any benefits to isotonic energy drinks when running a marathon (David Howells and Ron Maughan). We also hear from the new editor-in-chief of *Experimental Physiology*, Mike Tipton, who describes his work on extreme environmental physiology, and informs us (amongst many things) of how long to maintain a search for people lost at sea, given what is known about hope of resuscitation at different water temperatures.

There is an Irish emphasis in this issue (as I am the guest editor, and Irish, it is only fitting). Roger Thomas has a rapid report on the recent Dublin meeting of The Society in July, held in partnership with the American Physiological Society. The meeting was a great success with 1,200 attendees, excellent science, great views of Dublin city and mountains from the top floor of the Convention Centre, and thankfully very little rain. There is also an article on the past and present of physiology in the National University of Ireland, Galway (NUI Galway), my work abode (you have to take your publicity opportunities when you get them).

Post-Brexit vote, shock reverberates throughout the physiology community in Britain and beyond. Many of us fear that Brexit may create barriers to scientific collaboration, co-operation, endeavour and discovery in Europe as a whole. Gerta Vrbova's letter to the editor gives voice to her concerns, now that the vote for Brexit is a reality. In particular, she highlights her concerns that Brexit threatens the freedom of movement that underpins scientific co-operation. In a historical piece, she also highlights the negative impact of policies in Germany in the 1930s and 1940s on scientific endeavour and the exemplary efforts of AV Hill and other members of the international scientific community to rescue scholars at risk of persecution. However, on a positive note, the new formal link between our (The) Physiological Society, and the Scandanavian and German Physiological Societies is a very positive and welcome development. At least we have Europhysiology to look forward to in 2018.

This is my first attempt at guest editing – if you spot any mistakes, please send your letter of complaint to Roger, who will be back in the hot seat in the next issue!

Ad acta

Tim Biscoe
University of Bristol

In The Society's email sent on 31 March about the 140th Anniversary of The Society it was stated that The Society was 'making considerable contributions to the Animals (Scientific Procedures) Act 1876'. This statement was of course true for 1876, as you note, but the Procedures act was for 1986. Since a number of us spent around 5 years or more on this issue around the 1980s you should know that we are not so old as you imply. The others were in particular Ann Silver, Cecil Kidd, Jim Pascoe, and Denis Noble, Bernard Ginsborg, Tony Angel, and in general, those members of the Committee at that time, including the unwavering support of the Treasurers, Robert Comline and then Ron Linden. The leading MP for us all was Tam Dalyell who was enormously effective and helpful through two Private Members bills and eventually the Government proposed legislation. Tam Dalyell was supported in the Committee stages by Ray Mawby and Sir Nigel Fisher.

Note from editors: We apologise for the error occurred and confirm that this has been amended on our website.

Lessening the JIF impact

Michael Taggart
Institute of Genetic Medicine,
Newcastle University

At the Annual General Meeting of The Physiological Society, usually held in conjunction with the main scientific meeting, the attendees are given a summary of the activities in the previous year of each of The Society's journals. This seems to always involve, and Physiology 2016 was no exception, mention of the much-discredited Journal Impact Factor (JIF) and whether the 'value' had increased or decreased by a fraction of one point.

It may be apt to remind readers that The Physiological Society is a signatory to the San Francisco Declaration on Research Assessment (**http://www.ascb.org/dora; Twitter: @DORAssessment**). One of the central themes of this declaration is to remove/limit the pernicious influence of the JIF from all manners of research conduct.

Post-marathon photo
– thanks to The Society for the t-shirt!

Vital statistics

Age: 64 years, 4 months
Weight: 58.8kg
Body fat percentage: 14.2%
Resting heart rate: 44 bpm
Body water percentage: 61.6%
Official 2016 London Marathon finishing time: 3hrs 40min 31secs
Position in age category (60-64): 87
Overall position (men only): 7046th
Position overall (out of 39,008 finishers): 8,673th

Marathon Man

David Howells
Father of Sally Howells, Managing Editor, *The Journal of Physiology*

1. As an experienced marathon runner, I have several physiological questions, and wonder whether an energy drink would have saved the original marathon runner in 490 BC? In many ways the marathon is a ridiculous distance. Some say, a reasonably fit runner could cope with 20 miles relatively easily. But those additional six (and a bit) miles make the marathon a real challenge. The rationale seems to be that the human body typically runs low on carbohydrate as fuel after about 20 miles of running and resorts to burning fat. Is that right?

2. Over the years, I have experimented with taking on isotonic energy drinks and gels throughout the run. But frankly, I'm not convinced they made a real difference. This year I only had water - nothing else - and didn't feel any worse or better. My question is: all other things being equal, is there physiological evidence that so called energy drinks (or any other supplement, for that matter) stimulate the body to produce enough carbohydrate to last 26.2 miles? Or is it simply all in the mind?

3. I started running marathons in the early 1980s. The advice then was to drink lots of water. Concerns about the risk of dehydration abounded. Views have changed. My strategy for the recent marathon was to drink just water every five or six miles. I did feel a bit rough at about mile 23 (a mind issue?), but wasn't craving the sickly energy drinks at any time during the run. Maybe the more water one drinks, the more one craves for energy drinks to increase the concentrate of sodium in the body. Do we really need those energy drinks if we get our hydration levels right?

4. The roughest I have ever felt after a run was immediately following a 44 mile training run (back in the 1980s) when I was preparing for an 80 mile ultra run. I was well supported and took on lots (and I mean lots) of water about every five to seven miles. I felt ill for about three days. Someone suggested I needed to take salt tablets on the 80-miler (branded energy drinks were not quite as fashionable then). I did, and I have to admit that I experienced none of the same adverse effects.

5. Every time I have had a post marathon massage (courtesy of the MS Society for whom I usually run), my recovery has been very good (i.e. I can walk normally the next day). During the post-run massage this year, the physiotherapists were fascinated by my leg muscles, which were twitching wildly. It's something that I'm well used to, but gets more exaggerated after a long run. What causes this? I'd love to know.

My grateful thanks to all those at The Physiological Society who so generously supported the MS Society by sponsoring me this year.

Ron Maughan, Emeritus Professor of Sport and Exercise Nutrition at Loughborough University, wrote to the Editor in response:

1. There is some truth in the idea that fat is the main fuel after about 20 miles, but fat and carbohydrate are both used as fuels throughout the race. It is certainly true, though, that once the body's carbohydrate stores (glycogen in the liver and muscles) are depleted, high intensity exercise is not possible (Bergstrom *et al.*, 1967). We can run using almost entirely fat, but not at a fast pace. Training and dietary strategies are therefore generally aimed at using as much fat as possible to spare the limited glycogen (that's the training part), maximizing

glycogen stores before the start (that's the diet part) and then also consuming some more carbohydrate during the race. Remember that if you burn only fat, you need about 7% more oxygen than if you burn only carbohydrate: 1 litre of oxygen gives about 4.7 kcal on fat but about 5.0 kcal using carbohydrate. When oxygen supply is limited, burning carbohydrate makes sense. This has been known for a long time, but has been almost entirely forgotten (Zuntz, 1901)

2. Studies have generally shown that ingesting carbohydrate during exercise makes the exercise feel easier (as shown by Krogh and Lindhard (1920)) and can improve performance (as suggested by studies at the Boston marathon in the mid-1920's (Levine *et al.*, 1924) but not convincingly shown until much later. Within the last few years, some studies have shown that periodically rinsing the mouth with a carbohydrate drink and spitting it out can improve performance, even though none of the drink is swallowed (Carter *et al.*, 2004). Whether that is in the 'mind' or not, I am not sure, but there is no doubt that fatigue is more a matter of central nervous system function that of muscle function, as stated so clearly by Francis Bainbridge in his 1919 monograph of The Physiological Society which was and remains one of the best ever texts on exercise physiology (Bainbridge, 1919). Once again, this seemed to be forgotten by exercise physiologists of the latter part of the 20th century.

3. Most serious runners NEVER drink in training, even on long runs on hot days, unless they are practising their drinking strategy in preparation for a race. There is no obvious benefit to drinking in training apart from learning what works for you, to practise the mechanics of drinking and training the gut to cope with the presence of fluid while running. But remember that most energy drinks contain little or no electrolytes. The main electrolyte lost in sweat is sodium (and chloride) but the concentration varies greatly – anything from about 20-80 mmol/l (Shirreffs and Maughan, 1997). Most mainstream sports drinks contain about 20-35 mmol/l sodium – any more and it tastes salty. Remember that most of these are consumed as soft drinks, so taste is all-important. When sweat losses are very high, an Oral Rehydration Solution (ORS – intended for replacing water and salt losses in severe diarrhoea) may be more appropriate as these usually contain about 60-90 mmol/l sodium.

4. Drinking too much plain water will dilute the plasma sodium concentration and likely produce symptoms like those described. Very occasionally, it can be fatal, but you really have to drink a lot for that to happen (Hew-Butler *et al.*, 2015).

5. I'd love to know too! This sometimes happens before muscles go into cramp, but no-one really knows what causes cramp either. We have tried to find out, so maybe we can get you to volunteer for some experiments (Maughan, 1986).

Bainbridge FW (1919) The Physiology of Muscular Exercise. London Longmans, Green and Co

Bergstrom J, Hermansen L, Hultman E & Saltin B (1967). Diet, muscle glycogen and physical performance. *Acta Physiologica Scandinavica* **71**, 140-150

Carter JM, Jeukendrup AE & Jones DA. (2004). The effect of carbohydrate mouth rinse on 1-h cycle time trial performance. *Med Sci Sports Exerc* **36**, 2107-2111

Hew-Butler T, Rosner MH, Fowkes-Godek S, *et al* (2015). Statement of the 3rd International Exercise-Associated Hyponatremia Consensus Development Conference, Carlsbad, California, 2015. *Clin J Sports Med* **25**, 303-320

Krogh A, Lindhard JL (1920). The relative values of fat and carbohydrate as sources of muscular energy. *Biochemical Journal*, **14**, 290-363

Levine SA, G Burgess, CL Derick (1924). Some changes in the chemical constituents of the blood following a marathon race With special reference to the development of hypoglycaemia. *JAMA* **82(22)**, 1778-1779

Maughan RJ (1986). Exercise-induced muscle cramp: a prospective biochemical study in marathon runners. *J Sports Sci* **4**: 31-34

Shirreffs SM, Maughan RJ (1997). Whole body sweat collection in man: an improved method with some preliminary data on electrolyte composition. *J Appl Physiol* **82**, 336-341

Zuntz N (1901). Über die Bedeutung der versehiedenen Nährstoffe als Erzeuger der Muskelkraft. *Pfluger's Arch* **83**, 557-571

Our Fellow Members

Jonathan Coles
Institute of Infection, Immunity & Inflammation, University of Glasgow

The status of 'Fellow' of the Physiological Society discussed at the AGM sounds almost exactly the same as 'Member' 30 years ago. Maybe they should be selected in the same way: the candidate has to give a Communication which is discussed fiercely and there is a vote on whether the abstract should be published. This could replace workshops teaching students about correct presentation of results, and would also add some drama and excitement to meetings.

Brexit: obstacle to progress by ignoring the past

Gerta Vrbova
Faculty of Life Sciences, University College London

The vote to leave Europe has been a shock to most physiologists. This is perhaps not surprising since science benefits most clearly from international cooperation. The recognition of the international nature of scientific activity has been fought for by the distinguished physiologist AV Hill before and during the second world war. He and his colleagues believed that research is best served and most successful when there is cooperation between scientists from different countries and that support of such cooperation by governments and agents in power helps to promote research. There are many examples showing that science and physiology have benefitted from the freedom enjoyed by individuals to collaborate, exchange ideas and have the opportunity to move between different countries without restrictions. Brexit threatens this cherished liberty. There are many examples to illustrate the benefits of this principle of international cooperation, but the ideas behind it were clearly expressed by AV Hill both before and during the second world war.

In the 1930s in Germany and Austria the fascist governments perpetrated a policy that excluded Jewish scientists and other professionals from continuing their work. In England a group of academics including AV Hill expressed strong objection to this persecution. Hill had a strong belief that scientists have a special responsibility towards society and that this is linked with the international nature of science. In an article in Science (Hill 1941) he writes: 'It is nevertheless a fact that the nature of our occupation makes scientific men particular international in their outlook. In its judgment on facts science claims to be independent of political opinion, of nationality, of material profit. It believes that nature will give a single answer to any questions properly framed and that only one picture can ultimately be put together from the very complex jigsaw puzzle which the world presents. Individual and national bias, fashion, material advantage, a temporary emergency, may determine which part of the puzzle at any moment is subject to the greatest activity. For its final judgment however, for its estimates of scientific validity, there is a single court of appeal in nature itself, and nobody disputes its jurisdiction. Those who talk, for example of Aryan and non Aryan physics or of proletarian and capitalist genetics, as though they were different simply make themselves ridiculous.

For such reasons the community of scientific people throughout the world is convinced of international collaboration.' And later: 'In no other form of human activity, therefore, has so complete an internationalism spread throughout the national structure of society: in no other profession or craft is there so general an understanding or appreciation of fellow workers in other parts of the world. This implies no special merit or broadmindedness on the part of scientific men; it is their very good fortune, a good fortune which involves obligations as well as privileges. For example when the Nazis in 1933 began their persecution of Jews and liberals in Germany it was the scientific community in many other countries which came most quickly to the rescue of their colleagues; not out of any special generosity but because firstly they had personal knowledge of those who were being persecuted, and secondly they realized that such persecution struck at the basis of the position of science and scientific workers in society' and later : 'It may be then that through this by-product of international cooperation science may do as great a service to society (just as learning did in the Middle ages) as by any direct results in improving knowledge and controlling natural forces: not- as I would emphasize again- from any special virtue which we scientists have, but because in science world society can see a model of international cooperation carried on not merely for idealistic reasons but because it is the obvious and necessary basis of any system that is to work' (Hill 1941).

These views and ideas motivated Hill to become a founder member of the Academic Assistance Council (AAC) an organization that offered help to scientists persecuted in Nazi Germany and other fascist countries.

In 1933 whilst studying in Vienna, William Beveridge the director of the London School of Economics learned that academics deemed 'undesirable' by the Nazi government either because they were Jews or of a different political opinion than the Nazis were dismissed from their position and unable to work. Dismayed by this, Beveridge returned to England keen to help these scholars (Beveridge 1953). He established the Academic Assistance Council (AAC) which in 1936 became The Society for Protection of Science and Learning (SPSL) in 1939 Council for Assisting Refugee Academics (CARA) and finally in 2014 Council for at Risk Academics (CARA). This organization assisted academics forced to flee Nazi Germany, and later other countries ruled by Nazi Germany. He persuaded the prominent physicist Ernest Rutherford to become the first President and Hill Vice President of AAC.

In May 1933 Beveridge (Beveridge 1933) distributed a letter signed by many distinguished academics amongst them 5 Nobel laureates to publicize the new organization. The letter was published in major British newspapers. In June, Rutherford (Rutherford 1933) identified the charity's aims as twofold: 1/ to create a fund for academic assistance of displaced scholars, and 2/ to act as a centre of information, i.e. putting academics in touch with organizations that can best help them (Rutherford 1933). By the outbreak of the war the SPSL had aided at least 900 scholars. AV Hill's commitment to the organization that enabled scientists to continue scientific work was expressed in his letter to Beveridge on New Year's Day 1934: 'It is not that these people will perish as human beings, but that as scholars and scientists they will have to take up something else in order to live.' With hindsight and our present knowledge of the Holocaust this statement seems to have greatly underestimated the dangers and perils faced by these scientists, who would have perished had they not got out of the countries ruled by Nazi Germany. Thus by helping their colleagues, scientists in England more than any other intellectual group helped their colleagues to leave, continue to work and above all survive the Holocaust. This is in marked contrast to other professional organizations such as the medical or legal who for fear of competition did not offer help to their colleagues (Zimmerman 2006).

Scientific achievements are difficult to measure, but the number of Nobel prizes gives some indication. Before 1933 German scientists had won 33 prizes in science since 1900, the highest number of any nation, Britain won 18 and the USA 6. After Hitler's rise to power 7 Nobel Prize winners left Germany and 20 of the refugees subsequently obtained the Nobel Prize (Pyke 2000).

It is likely that by rescuing a generation of scholars from Nazi ruled Europe AV Hill and other members of the SPSL contributed more to scientific development in the West then any single individual could achieve (Vrbova 2003). Therefore AV Hill's views that international cooperation of scientists plays an important role for scientific achievement, have been confirmed. His contribution to bring about this cooperation while at UCL gives the college a special place in helping to initiate outstanding scientific developments in science and is consistent with UCL's liberal and secular values.

Brexit threatens these values and endangers the hard won freedom of scientific cooperation without frontiers. It is therefore pertinent that physiologists should remember one of their distinguished members and Nobel laureate, AV Hill, who championed these views under equally adverse conditions as those of today.

The views forged by AV Hill were accepted by many others in the west and helped to win the scientists the freedom to interact with each other even under most difficult conditions such as during the cold war. The cooperation between scientists from the Soviet Union and Russian-dominated countries and those from the west was an extraordinary example of the value of international cooperation. Making such interactions more difficult by restricting free movement as implied in Brexit is a dangerous backward step.

Beveridge Lord (1953). Power and Influence London Hodder and Stoughton, 234-235

Hill AV (1941). Science National and International and the basis of cooperation. *Science* **93**, 579-584

Rutherford Lord (1933). The British Academic Assistance Council. *Science New Series* **77**, 620-621

Pyke D (2000). Contributions by German emigrés to British medical science. *QJM* **93**, 487-495

Vrbova G (2003). Archibald V. Hill's contribution to science and society. *European Journal Translational Myology - Basic Applied Myology* **23**, 73-76

Zimmmerman D (2006). The Society for The Protection of Science and Learning and the Politicization of British Science in the 1930s. *Minerva* **2006: 44**, 25-45

Artistic merit

Lynn Bindman,
University College London

I was very amused by the menu doodles from the March AGM meeting, 1966. You didn't have an acknowledgement for the artist, perhaps because he wasn't known? I am sure the drawings are by Olof Lippold – I recognise the handwriting, the drawing style, and indeed the visual humour. There was a large framed cartoon drawing by Olof that used to hang on the Anatomy staircase at UCL. It was of a train of action potentials, one of which was forked at the top. In the top corner was a spider hanging by a thread – which had a knot tying up a break half-way down. Your readers might be interested to know the artist.

Question for the Editor or comment on a recent *PN* article?

Please send your correspondence to **magazine@physoc.org**

Jonathan Ashmore FRS receives The Royal Society's Croonian Award

Jonathan Ashmore, University College London

The Society wishes to congratulate Honorary member Jonathan Ashmore FRS, President of The Physiological Society 2012–2014, for being awarded the Croonian Medal and Lecture 2017, for his significant contributions to the field of sensory neuroscience, shaping our current understanding of inner ear physiology, in particular for his analysis of the role of cochlear hair cells in normal hearing.

This prize lecture is the premier lecture in the biological sciences and is delivered annually at the Royal Society in London.

The lectureship was conceived by William Croone FRS, one of the original Fellows of the Society. Among the papers left on his death in 1684 were plans to endow two lectureships, one at the Royal Society and the other at the Royal College of Physicians. His widow later bequeathed the means to carry out the scheme. The lecture series began in 1738.

2016 Annual General Meeting report

The 2016 Annual General Meeting (AGM) was held at the Convention Centre Dublin, Ireland on Sunday 31 July 2016. The meeting was chaired by Professor Brian Harvey, The Royal College of Surgeons in Ireland.

The meeting saw David Eisner appointed as President for a two year term.

The following members of Council stand down:

- Richard Vaughan-Jones (stood down as President)
- Blair Grubb (former Chair of Education & Outrach Committee)
- Judy Harris (former Deputy Chair of Education & Outreach Committee)
- Mary Morrell (former Chair of Policy Committee)
- Lucia Sivilotti

The Society offers thanks to these outgoing members of Council.

The four members elected to Council as Trustees for a four year term were:

- Federico Formenti
- Sarah Hall, Chair of Education & Outreach Committee
- Bridget Lumb, Deputy President
- Graham McGeown

Five individuals were awarded Honorary Membership of The Society. The new Honorary Members are:

- Annette Dolphin
- W Jon Lederer
- Ian McGrath
- Clive Orchard
- Wolf Singer

Our new Trustees will be introduced in the next edition of *Physiology News*.

Bringing you snippets of the latest intriguing research

Exercise may protect nerve cells

Long-term exercise appears to be beneficial for Spinal Muscular Atrophy (SMA)-like mice, suggesting a potential of active physiotherapy for patient care.

A 10-month training programme improved muscle resistance to activity-induced damages and increased aerobic performance in mice. While swimming and running was both beneficial for motor neurons affected by SMA, different types of exercise had an impact on different motor neurons and muscle fibers. Swimming protected intermediate and fast motor neurons (the most affected type of motor neuron in SMA), and enhanced the cross-sectional area of large muscle fibers, while running only protected slow motor neurons and enhanced the cross-sectional area of intermediate muscle fibers .

Physical exercise is known to induce benefits in some neurodegenerative diseases, including Parkinson's disease, but its benefits in other diseases such as Amyotrophic Lateral Sclerosis and Duchenne Muscular Dystrophy, remains controversial and highly debated for its routine use in patient care.

DOI: 10.1113/JP271361

Stress or being born small during pregnancy can lead to greater disease risk in mothers

Low birth weight or stress during pregnancy can lead to long-term health problems in women. The study found that stress during pregnancy leads to long-term health issues in mothers, affecting adrenal, metabolic and cardio-renal health after pregnancy. Study-leading PhD student Jean Ni Cheong, from The University of Melbourne, said it was known that being born of low birth weight or experiencing stress during pregnancy increased the ris of complications.

The researchers used a rat model where restricting oxygen, nutrient and blood supply during pregnancy led to offspring being born with a low birth weight. When these low birth weight female rats then became pregnant, researchers induced stress through common measurements performed during human pregnancy. Long after the conclusion of pregnancy, they studied parameters in the mothers including blood pressure, renal function, stress hormone production and metabolic function.

DOI: 10.1113/JP272212

Stem cell therapy as a potential treatment for severe burns

Scientists have discovered a new way to potentially treat muscle regeneration in patients with severe burns. The research, from The University of Texas Medical Branch, shows that while a severe burn injury causes cell death in the muscles, it also induces the muscle regeneration properties of specific stem cells (satellite cells, the resident stem cell in skeletal muscle cells). This highlights the therapeutic potential of satellite cells, allowing future studies to investigate ways to promote muscle regeneration and reduce muscle damage post-burn.

Researchers collected tissue samples from 12 patients with severe burn injuries and 12 healthy subjects. Immunohistochemical techniques were used to analyse and compare the satellite cell content, activation and cell death (apoptosis), as well as muscle fibre regeneration in the tissue samples. The researchers found that in burn patients, these cells are receiving a mixed signal, one that induces cell death and one which induces muscle regeneration.

DOI: 10.1113/JP272520

Longevity and human health may be linked to a muscle cell enzyme

A study has found that exercise and fasting do not change the location of a key enzyme involved in energy production.

SIRT3 is an important enzyme involved in fat metabolism and energy production. Located within the mitochondria of human skeletal muscle, it acts by targeting certain proteins and altering their activity. Nearly every cell in the body contains mitochondria as they are responsible for producing the energy cells need to function properly. Understanding the enzymes located in the mitochondria, their movements, and purpose in relation to the entire cell is essential for fully appreciating how cellular functions can influence the body's well-being.

To determine if SIRT3's location within muscle cells changes, healthy young men were split into two groups with one being subjected to endurance exercise for an hour and the other fasting for 48 hours. Skeletal muscle biopsies were taken at various time points post exercise and fasting and isolated the mitochondria. They found that although the level of SIRT3 mRNA in cells decreases, its location does not change, suggesting that its activity is not regulated by changes in its abundance within mitochondria in human skeletal muscle.

DOI: 10.1113/EP085744

EU Referendum Aftermath

There has now been a period for the result of the Referendum on EU membership, and the political ramifications, to settle in. The science sector has unfortunately been hit by immediate drawbacks, with the lack of certainty resulting in UK academics having to withdraw from EU funding applications and European researchers feeling unable to take up work in this country. The House of Commons Science and Technology Select Committee has begun an investigation into the implications and opportunities for science in leaving the EU, and the Science Minister has tried to offer reassurance to both the UK research sector and European science bodies.

Much analysis of the result has been inward-looking, questioning why the strong message coming from research, academia, and tech businesses was not heeded. While there is substantial bitterness (and considerable column inches) about Michael Gove's epitaph for the referendum: 'people in this country have had enough of experts', the truth is that 52% of the voting electorate were unmoved by scientists and economists. Organisations such as the British Science Association are working to understand the divide between science and the general population, and how to increase engagement with people who currently do not feel that science is working for their benefit. The Physiological Society is continuing its policy and outreach work, trying to engage with politicians and the public to express the importance of research into what makes us and how we work.

Parliamentary Links Day

Hot on the heels of the referendum result was Parliamentary Links Day. This is the main scientific event in the parliamentary calendar, attracting a capacity crowd and important speakers. The title of this year's Links Day was *Science After the EU Referendum: What Next?* – Having been planned a long time ago, the 'leave' result made the topic one of paramount importance.

The event was opened by Speaker of the House of Commons, John Bercow MP, a longstanding champion of science and technology. Speeches were also given by Jo Johnson MP, Minister for Science and Universities, and Nicola Blackwood MP, Chair of the House of Commons Science and Technology Select Committee. Ms Blackwood's speech, in particular, was very well received and directly addressed the concerns of those in the room, with more than a hint of emotion coming across. She discussed the shock scientists were feeling, and how a strongly-put case had not overcome distrust of 'the establishment.' She clearly expressed the message the scientific community needs to put out, saying 'we remain open for business, and are willing and reliable collaborators'. Finally, she called for scientific voices to be 'at the top table' in EU negotiations so the sector has direct input into the future relationship between Britain and the EU.

Panel discussions followed, with representatives of other political parties and key scientific bodies. Unfortunately, no Labour MP was present as the previous Shadow Science Minister, Yvonne Fovarge MP, resigned her shadow cabinet post. At the time of writing she has not been replaced. SNP science spokeswoman, Carol Monaghan MP, drew attention to the difference in perspective on science between UK and EU school students, saying those from the continent see more prestige in a scientific career.

The event was closed by Sir Venki Ramakrishnan, President of the Royal Society, whose speech struck a note of realism. He stated that Britain's 'influence in the world would decline if we stopped investing in science and technology', and that up to this point EU science funding had 'allowed us to remain competitive.' He called upon government to not only ensure investment in science is maintained, but that access to EU networks is retained to allow for future collaborations around the globe. He conceded, to wide agreement, that negotiations would be difficult, but that there was a clear goal for UK science.

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

A poem on the subject of Sleep Apnoea

By Ken O'Halloran *Department of Physiology, School of Medicine, University College Cork, Ireland*

I'm male and I'm old and a tad more than fat
And if that's not enough beyond all of that:
I'm sleepy, forgetful, it pains me to mention –
Erectile dysfunction; overt hypertension!
Disordered breathing is the trouble for me,
Pauses in airflow present frequently.
Sometimes as many as 60 per hour;
Throat muscles are knackered – can't generate power
Sufficient to open the pharynx you see
(That's a block of the pipe, when put quite simply).
My airway collapses, won't let nothin' through,
Damn thing is so common – one day 'could be you!

So what to look out for? Well snoring is key,
That's how it all started a while back for me.
And then the long pauses – silent interruption,
Before sitting up, as if a convulsion
Was triggered by dream, no rest for the weary...
Some wake up choking, now that is quite scary!

But worse than all that it progresses by stealth
And slowly but surely it worsens one's health.
Hell, life is a drag; I've considered narcosis,
Potentially better than atherosclerosis.
Ah...what am I saying, that's only conjecture,
You'll have to forgive my poor sleep architecture
Prevents me from having a normal day.
It's a pain in the ass – what else can I say?

See, the ticker is troubled and poor brain is muddled
And I'm starting to notice that both lungs are bubbled;
And I huff and I puff on account of the stuff,
And I wake in the morning feeling quite rough,
Only down to a sliver of functioning liver
I'm useless at work, it's too hard to deliver
Whilst struggling to pee with dodgy kidneys
This thing is a curse for them and for me.

And I was a poet, philosopher, dancer,
Now sleep doc' is saying this it could cause me cancer!
And that is the good news, if I struggle that far,
If the ticker don't blow out whilst driving the car.
See the cardinal sign is a person too sleepy,
By day, that is, at times it's quite creepy.
My missus resides now next door – the spare bed,
The snoring and snorting was wreckin' her head.

Sleep apnoea you say, so all's well whilst you're waking?
All's well, indeed, except for the aching
Muscles and joints, and general malaise
And most of my hormones all over the place.
Control out the window; bizarre appetite:
Increasing my girth, not helping the fight
Against this disorder which moves like a ninja,
So please think again before wagging a finger
At any one – of the one-in-ten?
Who are destined to join me – and that's not just men.

Yes ladies – one moment – for there is a clause,
The numbers are even once past menopause;
Indeed it's a syndrome for all shapes and sizes,
A large family – even athletes with prizes!
The rich and the poor, and the thick, and the thin
A mother, a daughter, or your next of kin
Could be lying in wait of a formal diagnosis,
And if something else, it could change that prognosis.

But wait, there is hope, in the glory we bask
Of gold standard treatment delivered by mask
CPAP is the hero, ostensibly
Though alas, despite trying, 'twas no good for me.
Though I worked with the docs in a hopeful alliance,
Their final conclusion? – Poor patient compliance!

So I tried excitation of nerve 'hypoglossal',
But most of the time it just caused me hassle.
So off to a surgeon who offered to me
A complex procedure – UPPP.
No thanks! So I search for that magic pill
Taken just before bed, which might keep my legs still
And allow me to dream, and to get some good REM
And to dance and to sing and behave more like them
Who sleep and then wake and arise with a smile
And lie with the missus at least for a while
And chat of the challenges – simple and scary –
And get on with it: a life ordinary.

So if you suspect, there's a friend, Gran or Dad
Who's sleepy, fatigued, and often quite sad.
You might, carefully, have a nice quiet word
Of a complex syndrome, of which now you've heard
Is silent but deadly, and hides in the wings,
The grimiest reaper who sets out to bring
Trouble on those who ought to be rested:
Get them down to the clinic so they can be tested!

Physiology at NUI Galway

Michael Kane

Retired, former Pre-clinical Vice-Dean and Head of Physiology, NUI Galway

Karen Doyle

Lecturer, Department of Physiology, NUI Galway

Antony Wheatley

Professor of Physiology, School of Medicine, NUI Galway

The Early Years

The National University of Ireland Galway was established under the Colleges (Ireland) Act 1845. The University was originally known as Queen's College Galway and was established, along with Queen's College Cork and Queen's College Belfast to offer non-denominational university education to the community. The Queens's College, Galway was later renamed University College Galway (1908) and later still National University of Ireland Galway (1997).

Queen's College Galway opened its door in October 1849 and students entered the Faculties of Arts (Literacy & Science divisions), Law and Medicine. Of the five professors in the Faculty of Medicine, Professor Charles Croker King was appointed Professor of Anatomy & Physiology, a post he held until 1863. He was succeeded by John Cleland who held the position until 1877 when he moved to the University of Glasgow to take up the position of Regius Professor of Anatomy, a post he held until 1909. Under Croker King and Cleland, the reputation of anatomy and physiology developed and attracted many students to Galway.

Professor Cleland was a renowned researcher and during his time in Galway he edited Quain's Anatomy (1867 edition) and was elected to a Fellowship of the Royal Society.

In 1877, Joseph P Pye was appointed to the combined Chair of Anatomy & Physiology, a post he held until his death in 1920. At this stage, independent chairs of Anatomy and Physiology were established and Joseph F Donegan became Professor of Physiology and remained in post untill he retired in1963. Thus two professors, Pye and Donegan, served physiology in Galway for 86 years. In his early career, Donegan had worked in the Physiology Laboratory under Professor Joseph Barcroft in Cambridge and also in the Institute of Physiology, University College, London, with WM Bayliss and EH Starling. He also worked in Berlin during two summer vacations and a sabbatical leave with two Nobel Prize winners, Otto Warburg and Hans Krebs. As Professor of Physiology, he taught, almost entirely on his own, not just physiology but also histology and physiological chemistry to medical students. Donegan was known to expect high standards from his students. A story told about him, possibly apocryphal but probably factual, illustrates this trait.

Professors Pye (left) and Donegan (above)

Students in the Physiology laboratory c.1910

One particular class of medical students (class size about 40-50) was very 'big into' rugby but not so 'big into' their studies of physiology and held the opinion 'He can't fail the lot of us!' Big mistake! A large majority of the students were failed and had to repeat the exam. He served on the Council of The Physiological Society from 1962 to 1966, and in 1976 he was honoured by The Society with the conferral of Honorary Membership.

The long service of these two professors in physiology was paralleled by the continuous service of two remarkable technicians, Thomas and Murt Hynes, father and son, for 80+years between about 1910 and 1995. Both were well-known long distance runners. Thomas Hynes had a road in Galway named after him. He represented Ireland in international cross-country races and marathons; in 1909, he was the first winner of a marathon organised in Ireland. He also fought in the Irish War of Independence 1919-1921. In a submission to the Irish Bureau of Military History, he recounted how he had been Quartermaster of the Galway Brigade of the Old IRA and, while on the run from the Black and Tans, often hid out at night in the Physiology Department in the UCG Quadrangle. His son, Murt, who succeeded him as chief technician, was a highly respected man of great integrity and scrupulous fairness. In athletics, he was a father figure in Irish long distance running. Making use of his athletic contacts, he pioneered the use of physiological testing on leading Irish athletes at UCG in the late 1960s early 1970s.

Physiology at NUI Galway: 1960–2000

After Professor Donegan's retirement in 1963, Dr JK (Kieran) Burns was appointed Professor of Physiology. Professor Burns was an unconventional physiologist with an interest in the interaction of science and religion. His individual approach to research was not always well received by the Members of The Physiological Society at its annual meetings. He retired from the University in 1991.

In the early 1960s, Burns was joined by two academic colleagues, firstly Dr Dom Colbert, the author of *Fundamentals of Clinical Physiology* (Prentice Hall, 1992) and *MCQs in Basic and Clinical Physiology* (OUP 1996). Dr Colbert also had a longstanding interest in travel and tropical medicine. In 1977, he founded the Voluntary Service Abroad society and worked extensively in Africa, the Far East and the Caribbean in a voluntary capacity. He received many honours including an honorary fellowship from COSECSA (College of Surgeons of East Southern and Central Africa) in 2013. Dr Daniel O'Donovan also joined the Department in the mid-1960s. He was a renal physiologist who had gained his PhD at the University of Rochester working with Professor RF Pitts. Much of his work was concerned with acid-base balance and the kidney particularly the role of glutamine metabolism. He was promoted to Associate Professor in 1976 and was awarded the Conway Medal for Research from the Royal Academy of Medicine in Ireland in 1984. He retired in 1997.

In 1976, Dr Michael Kane, a reproductive physiologist, was appointed lecturer and went on to be promoted to Associate Professor (1991) and appointed to Professor of Physiology in 1995, 4 years after Professor Burns retirement. His two major areas of research interest were preimplantation embryo growth and ovarian follicle development. He was awarded the Conway Medal in 1990, a DSc from the National University of Ireland in 2005, elected a member of the Royal Irish Academy in 2007, and awarded the Marshall Medal from the Society for Reproduction and Fertility in the UK 2016. At the time of the start of Professor Kane's tenure as Head of Physiology in 1995, teaching in physiology was almost entirely limited to medical students and laboratory teaching facilities were in a very poor state; there was an almost total absence of modern student laboratory equipment and smoke drums were still being extensively used in student laboratory classes. A major priority of Kane's tenure as Head of Physiology was the improvement of physiology teaching, especially laboratory teaching. As Pre-clinical Vice-Dean, Professor Kane oversaw the re-organisation of the first two years of the medical course so that the former discipline-based teaching was replaced with integrated module based teaching by the preclinical departments of Physiology, Anatomy, Biochemistry and Pharmacology.

‘Despite having gone through some difficult times, the future of physiology is looking bright’

The Quadrangle building c.1800

NUIG Physiology – the years of expansion

In decade from the late 1990s into the 21st century, NUIG went through a transition from being a small institution on the west coast of Ireland into a modern medium-sized university (±17,000 students) catering for both local and international students. In addition, the College of Medicine, Nursing and Health Sciences was an established lead in teaching and research in the Institution. The expansion of the medical programme, the arrival of increasing numbers of health science students and the increasing popularity of physiology among Science students led to an explosion in the volume of teaching Physiology staff had to carry. Much of the teaching load in this time was carried by four enthusiastic young lecturers, Ailish Hynes (endocrinology), Leo Quinlan (epithelial physiology/electrophysiology), Karen Doyle (neuroscience) and later Michelle Roche (neuroscience), and helped by an excellent technician, Barbara Coen, who had previously worked in the Physiology Department at Charing Cross Hospital. The research of the Department benefited from the fact that, in addition to local Irish funding over a number of years in the 1990s and early 2000s, Professor Kane and other Departmental members were able to obtain considerable research funding via a number of European Framework programmes. However, the huge teaching load of the Department was a serious hindrance to research at this time and the work of the Department was inhibited by a long failure to provide alternative facilities to its cramped quarters in the old University Quadrangle.

In 2009, Antony Wheatley (liver and cardiovascular physiologist) was appointed Professor of Physiology, following the retirement of Professor Kane in 2006 and there followed additional appointments, Louise Horrigan (immunology), Amir Shafat (human physiology), Karl McCullagh (muscle), Beth Mallard (liver and gastrointestinal physiology) and Brendan Higgins (lung injury). For further information about our research programmes, please consult our departmental webpage (**www.nuigalway.ie/physiology/**).

The future

Despite having gone through some difficult times, the future for physiology is looking bright. Firstly, we are still an autonomous department within the School of Medicine, with control over our teaching and research activities. Secondly, after years of being poorly resourced (our departmental administration is still in the University Quadrangle; I guess we have been there since 1847) we are on the threshold of moving into an 8000m2 new teaching/research building along with the Departments of Anatomy and Pharmacology & Therapeutics. It is anticipated that the new building will open its doors before the end of 2016. The new building will house the University Bioimaging Centre, an animal behaviour suite and more than 1000m^2 of additional research laboratory space. The future of Physiology at NUI Galway is looking bright.

A Celebration of Education Focussed Careers: A review of *Recognising Teachers in the Life Sciences*, published by The Physiological Society

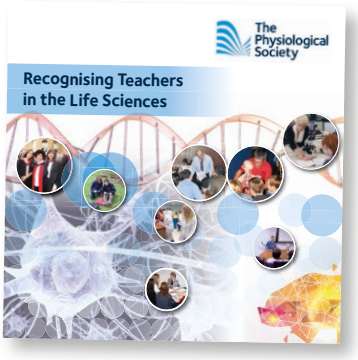
Katharine Hubbard

School of Environmental Sciences, University of Hull, UK
Royal Society of Biology Higher Education BioScience Teacher of the Year 2016

The Pphysiological Society's *Recognising Teachers in the Life Sciences* is availble from: https://www.rsb.org.uk/careers-and-cpd/careers/career-resources

Inspiring and training the next generation of Biologists is one of the most important activites undertaken in universities, and can be one of the most rewarding. However, the role of teaching in UK universities is coming under increased scrutiny with the forthcoming Teaching Excellence Framework (TEF), which may include metrics to assess how institutions 'encourage and reward excellent teachers'. The lack of parity between education- and research-focussed careers in Higher Education has been repeatedly highlighted. I know of many early career academics who have been told that there is 'no such thing' as a teaching career in higher education, despite the clear need for high quality teaching throughout the sector. To raise the profile of biology educators, The Physiological Society, in collaboration with the Academy of Medical Sciences (AMS), Royal Society of Biology (RSB) and the Heads of University Biosciences (HUBS) have published *Recognising Teachers in the Life Sciences* which highlights the careers of academics for whom promotion has been achieved primarily through teaching.

The glossy booklet profiles 32 education-focussed academic in the life sciences from a range of institutions including Russell Group and post-92 universities. Each case study includes a career timeline, a list of professional memberships, awards and prizes and a short interview with the academic about their career development. All started their careers with biology PhDs or equivalent professional qualifications, and now work in a diversity of teaching roles. Some are now exclusively education focussed while others combine significant teaching activities with discipline-based research. 20 of the contributors are professors, most have won awards for the quality of their teaching and several are National Teaching Fellows. The case studies also highlight the range of scholarly contributions or leadership roles of the contributors, who include grant holders, text book authors, journal editors, Directors of Learning and Teaching, Associate Deans and Pro-Vice chancellors. What is most striking about the contributors is their passion for and dedication to education;



many participants discuss how teaching was significantly more personally rewarding than research, and that it was an active choice to develop an education-focussed career. The booklet therefore provides a series of much needed role models for those wanting to develop an academic teaching career, and celebrates the contributions of those who inspire the next generation of biologists.

However, the most important material comes at the end, which lists 'Top tips' for advancing an education-focussed career collated from the contributors. These emphasise the message that building a career takes more than excellent classroom teaching, but also requires developing a profile outside of your institution, taking on positions of leadership and building a portfolio of evidence to demonstrate commitment to education.
A related project from the RSB and The Physiological Society has recently established a Teacher Career Progression Framework to help education-focussed academics align such activities with promotion criteria. While *Recognising Teachers in the Life Sciences* rightfully celebrates the achievements of some of our best bioscience educators, its real value will come through providing examples of successful teaching careers to individuals looking to advance, but also to university promotion panels and policy makers. Ensuring reward and recognition applies equally to those on teaching and research contracts will only become more important in the UK Higher Education sector, and this collection of inspiring case studies is a small but very welcome contribution.

Ground control to Major Tom

Floating in microgravity on a Parabolic Flight

Julia Attias
Research Student,
King's College London

Whenever I am approached with the question 'What do you do?' , I often find myself responding, 'Have you got five minutes?'. Not because I want to talk about myself incessantly, but because it often takes that long to explain what I do. Replying with 'I'm a space physiologist' just doesn't seem to cut it. Most either say 'Huh? What's that?', or give me a bewildered look coupled with stunned silence, so I end up providing a necessitated lengthy explanation.

On the one hand it's pleasant, because it means my work is unique and novel. On the other hand, it's frustrating, because it leads me to believe it's not important enough to be well-known. Admittedly, I didn't know about the field of space physiology myself until 2011. Being always interested in extreme environmental physiology, I stumbled across the Space Physiology and Health Masters at King's College London online, and only then did it dawn on me that it was a 'thing'.

The UK's contribution to spaceflight has historically been technology-based; satellites are one of the UK's best offerings for the space sector. Tim Peake's very recent mission to the international Space Station has not only helped immensely to put space physiology on the map – and in doing so make people understand what individuals like myself do – but has also led to the government recognising that we need an expanded space programme (which in turn will enable a wider understanding of what we do, and why we do it).

So what is a space physiologist and why are we important? As physiologists, we understand the parallels between physiology in hostile environments and clinical populations such as altitude and chronic obstructive pulmonary diseases, i.e. hypoxia as the common denominator. Microgravity environments are no different. In fact, there are numerous clinical populations that can be studied and understood using this paradigm, and ones we can all relate to.

The most problematic aspect of microgravity environments is the absence of loading. Gravity produces mechanical loading that plays a fundamental role in regulating the health and function of numerous physiological systems. In particular, the musculoskeletal, cardiovascular and neuro-vestibular systems are all highly dependent on gravity for the maintenance of normal function.

Photo shot by the BBC of the research of the SkinSuit team, with my colleague Phil Carvil and supervisor Dr David Green

SkinSuit team during our Parabolic Flight campaign, supported by the Space Medicine Office

Certificate from IAAGMOOH

Within the first 48 hours of entrance into microgravity, fluid is displaced from the lower body to the upper body, causing a loss of approximately 8-10% of plasma volume (hypovolemia), in part due to increased water excretion via the kidneys. Hypovolemia reduces ventricular filling, stroke volume and thus cardiac output, in addition to concurrent reduced erythropoietin production. Such changes are likely to contribute to orthostatic intolerance, increased venous distensibility and aerobic capacity decrements upon return to Earth. Terrestrially based individuals suffering with postural hypotension or those with malfunctioning sympathetic adrenergic vasoconstriction are also subjected to decreased orthostatic tolerance.

The consequences of un-weighting on the musculoskeletal system displays a hierarchy in relation to muscle and bone most relied upon for maintenance of the upright posture. Loss of muscle volume and cross sectional area have been widely documented from spaceflight and bed rest studies of varying durations, ranging from decreases in triceps surae volume of 6% after 8 days, to ~24% in gastrocnemius volume after missions <100 days, thought to result from a reduced protein synthesis and exaggerated breakdown, with an emphasis on the former. Muscle strength decrements couple these volume decrements.

Femoral neck and total femur have been shown to lose 1.4% and 1.5% bone mineral density per month respectively, thought to result from reduced bone formation as a consequence of osteoblast dysfunction and excessive osteoclastic resorption. This increases fracture and renal stones risk, with bone architecture taking over one year to recover. Studies involving bed rest, Unilateral Limb Suspension (ULLS), and immobilisation, have showed analogies in musculoskeletal size and function facts and figures.

Clearly there is a bigger picture here; this is not just about the physiological de-conditioning of astronauts, but a large number of terrestrial populations, including, but not limited to those who are detrained, have sustained injuries, are in intensive care, have spinal cord injury, have casted limbs and so on. Let us also not ignore the analogies to multiple cardiovascular dysfunction and musculoskeletal atrophy disease states, and although are pathogenesis-dependent, must be considered.

As such, countermeasures employed to tackle these issues during spaceflight have just as much validity for these individuals on Earth. The work I do is a collaborative endeavour with the Space Medicine Office at ESA, MIT and of course King's College London, and focuses around researching (by means of a PhD) with a skin-tight garment designed to provide a low degree of axial loading (~20%), in an attempt to help mitigate some of this deconditioning in space and Earth-based populations.

It's hugely important to me to promote what I do to the wider community. It's one thing being a scientist in a field so niche that isn't well known; it's another being a female scientist attached to historical stigmas and stereotypes. Whilst I have been fortunate enough to not face many barriers, and work for an institution that wholeheartedly promotes gender equality through the Athena Swan program, I know many that have been discouraged out of studying STEM subjects (and not only females might I add; those with disabilities too).

On top of working towards my PhD, I undertake a fair amount of outreach in an attempt to do my part to change that. I often attend schools, and talk to the pupils about what I do, and what else science has to offer. To show them that it isn't just about Bunsen burners and photosynthesis – which is all I really remember from school, though thoroughly enjoyed nonetheless – but that there is a bigger Science picture. I also point out that whether you study medicine, engineering, cellular biology, chemistry or psychology, the beauty of science is the overlap to all of these disciplines, and we couldn't do anything without a collaboration of all of these entities.

I entered a competition called 'I'm an astronaut get me out of here', which involved talking to school pupils on live 30-minute webchats over two weeks about questions they had relating to Tim's mission. The students voted for their favourite 'expert'; I was privileged to win their vote and was filled with pride from the fact that I had obviously gotten through to them, which has only fuelled me to continue. I also write blogs for GlamSci – a charity set up by a disabled female who was told she couldn't pursue science through her entire academic life – to help inspire people from all walks of life to pursue STEM subjects.

I will continue doing outreach for as long as my time and energy permits. My other aspirations are to set up a YouTube channel to post science tutorials and interviews with scientists renowned in their fields, set up forums and workshops for teachers/academics who wish to impart space physiology knowledge onto their respective students, and collaborate with other scientists and institutions to raise STEM awareness to as many people as possible. I am always open to ideas so please get in touch with me if you have an idea that you would like to share. Alternatively, you can catch me on the Discovery Channel in September, in a TV series called 'Meet the Superbrains'.

Cold, Wet & Nasty

The new Editor-in-Chief of *Experimental Physiology* talks about his research background in immersion–related death

Mike Tipton

Extreme Environments Laboratory, Department of Sport & Exercise Science, University of Portsmouth & Editor-in-Chief of *Experimental Physiology*

I am delighted to be taking over this important journal from October 2016, after shadowing outgoing Editor-in-Chief Paul McLoughlin. *EP* recently published my G.L. Brown lecture (Tipton, 2015), although this was not part of the deal!

I have spent a large proportion of my career trying to help reduce the global burden of immersion-related deaths. The latest WHO estimation, probably an under-estimation, is that about 42 drownings occur per hour around the planet. Drowning is the second most common cause of accidental death in most countries; in the UK we lose a child a week and between one and two adults a day to drowning. Our contribution has been to try and understand the physiological and pathophysiological responses evoked by immersion. This has also involved working closely with important end-users such as Surf Lifesaving GB, the Royal National Lifeboat Institution, the Royal Life Saving Society, the Fire & Rescue Service and Her Majesty's Coastguard.

My interest in extreme environmental physiology started with the King's College, London MSc. in human and applied physiology in 1982. It involved visiting a wide variety of research centres. It was during a visit to the Institute of Naval Medicine in Gosport that I became really interested in thermoregulation, in particular how it related to survival in the sea. Dr Frank Golden was running an experiment that involved swimming for up to 20 minutes in water at 5°C wearing normal clothing; I vividly remember the cold-pain and respiratory drive associated with entering the water!

A lifelong friendship and collaboration with Frank Golden followed until his death in 2014, and a profound interest in how and why change stimulates the body, specifically the dynamic response of cutaneous thermoreceptors. When we started, and as a result of the Titanic disaster, the widely-held belief was that hypothermia (deep body temperature <35°C) was the major threat presented by immersion in cold water (thermoneutral water temperature in which you can sit without heating or cooling is 35°C. Cold water has no strict definition but is generally regarded as being below 15°C).

Our early work identified 'cold shock' – the cardio-respiratory responses evoked by sudden cooling of the skin – as the first and greatest threat to those immersed in cold water, with the pathological outcome being drowning rather than hypothermia (Tipton, 1989). Further mechanistic work into the early responses to immersion, hypothermia, circum-rescue collapse and the efficacy of basic life support with immersion victims, was complimented by research looking at mitigating the threat associated with cold shock by physiological and technological means. This included studies into cold habituation, and the development of both the first helicopter underwater emergency breathing system for offshore oil industry passengers in the UK, and an 'integrated survival system' for those flying over water in helicopters (Tipton *et al.*, 1995). More recently we have looked at the mechanisms that might act as the pre-cursor to sudden cardiac death on immersion in cold water as well as other circumstances, including 'Autonomic Conflict' – brought about by the coincidental and conflicting acute activation of the cardiac components of the cold shock response (tachycardia) and diving response (bradycardia) (Shattock & Tipton, 2012). We are currently exploring this topic further in collaboration with Prof Mike Shattock's cardiology group at King's College.

It's not all doom and gloom; part of our work has considered why some individuals, particularly children and small adults, occasionally survive long periods of submersion – the current 'record' is 66 minutes of submersion with complete recovery. Our proposed mechanism involves selective brain cooling caused by the two minutes of underwater breathing (heat exchange) associated with the drowning process. This is not just of academic interest; search and rescue organisations want to know how long they should search,


Mike Tipton

particularly when they are at risk themselves. The answer seems to be up to 30 minutes when the water is warmer than 6°C and up to 90 minutes when it is fresh water and colder than 6°C (Tipton & Golden, 2011).

My enthusiasm for integrative physiology has also led to research aimed at investigating whole body integrative responses to environmental stressors, as well as a call for more multi-environmental stressor studies and studies on cross adaptation (Tipton, 2012). Like many other areas, those working in extreme environmental physiology tend to become pigeon-holed as experts in 'cold' or heat' or 'altitude'; occasionally it is good to step back and look at what happens when these stressors combine acutely and chronically, as they do in the natural world. Other work has focused on cold injury, heat and hypoxia as well as physical employment standards for those working in extreme environments. The common approach has been to gain an understanding of the basic physiology underlying environmental hazards, and use this knowledge to select, prepare and protect those confronting these hazards.

I am delighted to be taking over as EiC of *EP* from Paul; he has done a selfless, first class job over the last five years. I think it will be a challenging and interesting job at a challenging and interesting time for science and scientific publishing. The charge (in every sense) towards open access publishing and an increase in the number and type of journals brings competition and raises fundamental questions about the communication, veracity and reproducibility of scientific findings. There has also been a shift in where physiology is practised, from medical schools to other university departments and institutions. On my travels I see physiologists doing excellent work in a wide range of circumstances including for elite sport, the military and different industries. Sir Peter Medawar once said that the dinstinction between 'pure' and 'applied' science is false. There are only two types of science; 'good' and 'bad'. In such times of change we must continue to be innovative and responsive in helping scientists, wherever they ply their trade, to communicate their high quality findings.

EP has many strengths: it has a long and distinguished pedigree; it has a reputation for excellence; it is a product of, and therefore closely associated with, the Physiological Society; it has high quality sister publications. It is these attributes that attracted me to the position of EiC and which I hope we can use to ensure that *EP* becomes the journal of first choice for the increasingly diverse family of scientists undertaking first class, novel physiological and pathophysiological experimental research into homeostatic and adaptive responses in health and disease, exercise, ageing and, of course, environmental challenges. (**http://physoc.onlinelibrary.wiley.com/hub/journal/10.1111/(ISSN)1469-445X/aims-and-scope/read-full-aims-and-scope.html**).

'*EP* has many strengths: it has a long and distinguished pedigree; it has a reputation for excellence'

References

Tipton MJ (2015). GL Brown Lecture: 'Extreme Threats' Environmental extremes: origins, consequences and amelioration. *Experimental Physiology*. http://onlinelibrary.wiley.com/doi/10.1113/EP085362/full.

Tipton MJ (1989). The initial responses to cold-water immersion in man. Editorial Review, *Clinical Science* **77**, 581-588

Tipton MJ, Balmi PJ, Bramham E, Maddern T & Elliott DH (1995). A simple emergency underwater breathing aid for helicopter escape. *Aviation Space & Environmental Medicine* **66**, 206-11

Shattock M & Tipton MJ (2012). 'Autonomic conflict': a different way to die on immersion in cold water? *Journal of Physiology* **590(5)** (Pt 14), 3219-30

Tipton, M. J. & Golden, F. St.C. (2011) Decision-making guide for the search, rescue and resuscitation of submerged (head under) victims. *Resuscitation* **82**, 819-824

Tipton MJ (2012). A case for combined environmental stressor studies. *Extreme Physiology and Medicine*. doi:10.1186/2046-7648-1-7

2016 *Forthcoming events*

14 November

GL Brown Prize Lecture:
New biomaterials for regenerative medicine and early detection of disease
Hodgkin Huxley House,
London, UK

www.physoc.org/glbphysfri/

15 November

H^3 symposium - Gene Editing and Gene Regulation with CRISPR
Hodgkin Huxley House,
London, UK

www.physoc.org/crispr/

13 December

Pharmacology 2016 – Organ-on-a-chip technology – the future of physiological profiling
QEII Conference Centre,
London, UK

www.physoc.org/bps-2016/

1 August 2017

IUPS 2017 – The Rhythms of Life
RIOCENTRO Exhibition & Convention Centre

www.physoc.org/iups2017/

Meeting Notes

Physiology 2016: Joint meeting of the Physiological and American Physiological Societies

29–31 July 2016,
Convention Centre Dublin, Ireland

Roger Thomas

Editor, *Physiology News*

Convention Centre Dublin

This joint meeting was held in the Dublin Convention Centre from 29–31 July. The Centre is an impressive new building on the North bank of the Liffy River next to the elegant Samuel Beckett bridge, with plenty of space for the over 1,200 people attending. There were plenty of staff in the building, and each hall was equipped with the latest audio-visual equipment and up to four operators. Only very rarely did I hear the cry 'How do I start my powerpoints?'.

The meeting started with a pair of plenary lectures from Jeffrey Friedman about Leptin and Jon Lederer about calcium in the heart, and ended with one from Bert Sakmann about Neuronal Networks. In between there were ten more plenary, keynote or prize lectures, including one from John O'Keefe, and twice a day six parallel sessions of symposia, and many workshops and two huge poster sessions. The total of posters was over 700, including about 30 described as late-breaking. It was difficult to do justice to the vast amount of information being presented.

The President launched his report on physiology

On Saturday a report on the 'Health of Physiology' was presented by the outgoing President Richard Vaughan-Jones. He urged his audience to take home and read the 40 page document and become more involved in

promoting the subject. It is still not widely appreciated how central the subject is to modern medicine. That evening the Society Dinner was held for over 400 members and guests in the Double-Tree Hilton ballroom in central Dublin. Coaches to and fro were provided. The menu was impressive: a starter of goats (sic) cheese parcel, with ham, watermelon and a beetroot puree, followed by a Munster Fillet of Beef with what seemed to be a cube of polenta, and finished with three mini desserts on a long plate. Altogether washed down with plenty of wine and finished with coffee and speeches. Considering the numbers, the food was very good and well served, and the whole occasion a great success, even though it concluded with an entertainment.

The Annual General Meeting of The Physiological Society

The third day included the AGM., held over lunch-time. I can briefly report that the new council members elected were Federico Formenti, Sarah Hall (ex-member of the *PN* editorial board), Graham McGeown and Bridget Lumb. The last will be the Society's new Deputy President, and will succeed David Eisner as President in 2018. She will be the Society's first woman President! Richard Vaughan-Jones, the outgoing President, then spoke about the years events, and Anne King the treasurer told us that all was financially sound. The members then had to vote to amend the Articles of Association, as previewed in *PN* 103. The vote was essentially unanimous, though some doubt was expressed about the proposed new category of membership - a Fellowship.

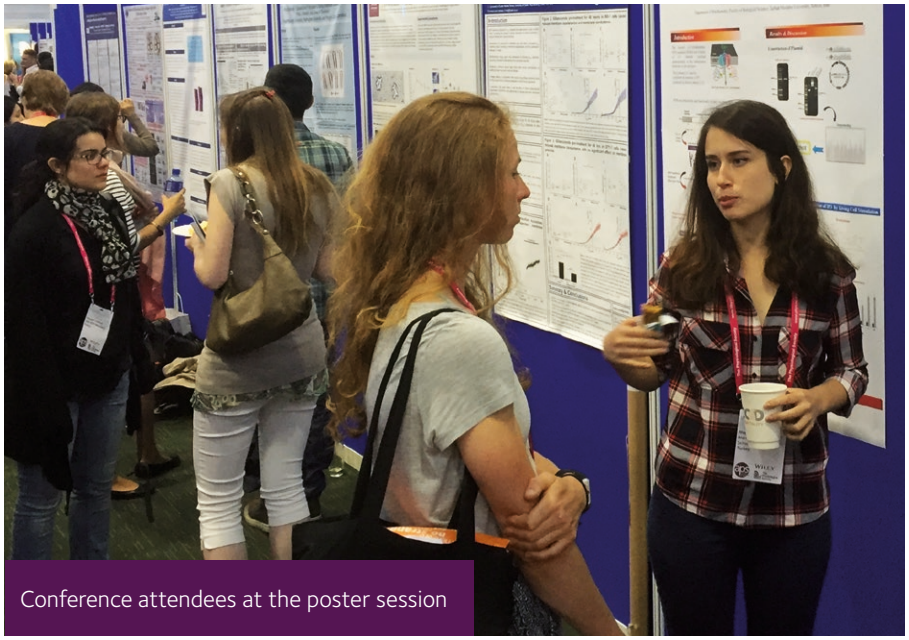
After the excitement of an important vote, we had reports by or for the editors of the Society's four publications. Kim Barrett for the *Journal of Physiology*, Paul McLoughlin for *Experimental Physiology*, Prem Kumar on behalf of *Physiological Reports*, and myself very briefly for *Physiology News*. Time had run out, so we had no proper discussion of the time and place of the next AGM. Sometime in July or August 2017, either in Rio de Janiero or London, probably.

Early Career Meeting

The main meeting had been preceded by a one day meeting for Early Career Physiologists. It was organised by Natalia Lajczak and Sinéad Quinn of the RCSI and Paul Cherry of the University of Ulster. My source tells me that it was a huge success with over 100 attendees. A high calibre of abstracts were received from across several of the Physiological Society themes. The highlights of the day were the keynote lecture from Dr Robert Tarran highlighting the effect of smoking on CFTR and a unique and personal perspective of chloride transport in smooth muscle in Prof. Otto Hutter's plenary lecture.

Altogether Dublin provided reasonable weather and fine hospitality. I particularly enjoyed the gleaming new red tram line which ran right behind the Convention Centre. Buses to and from the airport were frequent and cheap.

Emma Hart being presented with the Sharpey-Schafer prize after her lecture



Conference attendees at the poster session

Otto Hutter with Paul Cherry, Sinead Quinn and Natalia Lajczak, organisors of the Early Career Physiologists Symposium (ECPS) 2016

From the Archives: minutes of meetings 50 years ago, written by the then Meetings Secretary, EJ Denton

Transcribed by Roger Thomas

The Physiological Society, Institute of Physiology, Glasgow University, 23–24 September 1966

A meeting or The Society was held in the Institute of Physiology, Glasgow University at the invitation of RC Garry, on the 23 and 24 September at 11 am. Beginning at 11am on Friday the 23rd with RC Garry in the chair, leisurely start was made with five papers before lunch. In the afternoon, partly because of an increase in pace and partly through the withdrawal of Communication 9, the programme was up to time by tea. After tea a large number of demonstrations, including four extra, fully occupied the attention of members until 6:30 pm, when the University very kindly provided sherry in the Randolph Hall, where The Society was welcomed by Sir James Learnsonth on behalf of the University Court. During the sherry hour the adjacent Hunterian Museum was open, with exhibits ranging from local relics marking the northern-most outpost of the Roman invaders (halted, according to one of the Secretaries, not by the resolute resistance of the natives but by a realistic appreciation that it was not worth going further) to a fine collection of paintings by Whistler.

The Society dined and wined in the new refectory, the wine being provided and poured by members of the staff of the Institute of Physiology. After dinner, GL Brown thanked their host on behalf of The Society for a very pleasant meeting, and drew members' attention to the great changes, which had taken place in the Institute of Physiology, improvements of which the chairman, BC Garry, might rightly be proud. This was echoed by CF Code in a short speech on behalf of overseas members. BC Garry, in reply, assured The Society that only their imminent arrival had ensured the department being so advanced in its alterations, and hoped that in a year or two, when these were complete, the Institute would again have the pleasure of entertaining The Society. Friday evening ended with a film show including still pictures from the Tokyo Congress by GR Hervey. The Tokyo film was unfortunately not available.

On Saturday, members first visited the Hyperbaric pressure chamber in the Western Infirmary, followed by a short Semi-annual Meeting beginning at 11:20. On the proposal of E Benton, Sybil Creed and T Scratcherd were elected Scrutineers, and they later announced that all those in the ballot had been elected. The programme for 1967 was accepted. At 11.30 am, with IA Boyd in the chair, the remaining communications were heard. After lunch, The Society visited the Veterinary Hospital and the Wellcome Research Laboratories at Garscube for a very interesting programme of demonstrations. The meeting ended with tea at 4.30 pm.

Friday 23 September: Coffee 150, Lunch 110, Tea 180, Dinner 164

Saturday 24 September: Coffee 150, Lunch 102

The Physiological Society, Joint National Institute for Medical Research, Mill Hill 4–5 November 1966

At the invitation of B Delisle Burns, a meeting of The Society was held at the National Institute for Medical Research, Mill Hill, on the 4 and 5 November, 1966. On the Friday morning, beginning at 11 am, a very successful programme of demonstrations was arranged by OG Edholm at the MRC Laboratories, Hampstead, attended by 170 members and guests. It is twenty years since The Society had visited the Holly Hill Laboratories; Mill Hill was then still in the hands of the Admiralty and all of the MRC activities were closeted at Hampstead. Human physiology is now the main interest, and the demonstrations showed how vigorously this is pursued. Men and women, were placed in confined spaces, hot air blown at them, pumped round them, and even their own hot air looked at. Their heart rates, respiration, muscle activity, brain waves, even the indelicate gurgles of their gut were measured, and all displayed to us in an extremely lucid way. On the Friday afternoon, beginning at 2:30 at Mill Hill with B Delisle Burns in the Chair, nine communications were heard before tea, and with W Feldberg as Chairman a further five papers after tea.

After Dinner, which was held in the Institute, JL Malcolm thanked B Delisle Burns and his colleagues on behalf of The Society and expressed The Society's pleasure both on the return of an old colleague and emigre as head of the division and on the continuing presence of W Feldberg, who was so associated in members' minds with these Mill Hill meetings. B Delisle Burns, in reply, welcomed The Society and its guests and entertained them with an account of the differences he noted between science on the two sides of the Atlantic; on this side, we appear to be able to retain formality under the most unlikely circumstances.

On Saturday, with O G Edholm in the Chair, the remaining nine communications were given, and the meeting ended, as is the custom at Mill hill, with demonstration. Demonstrations in the afternoon until tea at 4:30 pm. There was one extra demonstration.

Friday 4 November: Lunch 70, Tea 284, Dinner 156

Saturday 5 November: Lunch 160, Tea 64

The Physiological Society, St Bartholomew's Hospital Medical School, 16–17 December 1966

At the invitation of N de Burgh Daly, a meeting of The Society was held in the Physiology Department of St. Bartholomew's Hospital Medical School on h 16 and 17 December 1966. Beginning at 2:30 pm on Friday, with M de Burg Daly in the chair, six papers were heard before tea. This was followed by a very full programme of demonstrations, several of which were of the risky, live variety, though all - at least to the visitor's eye - were models of the calm, controlled experiment.

After dinner in the splendid Great Hall of St. Bartholomew's Hospital, SL Stone, on behalf of The Society, thanked N de Burgh Daly for a very pleasant meeting and the Governors of the Hospital for allowing The Society the use of the Great Hall. He was not clear on what grounds he had been chosen to propose the

vote of thanks and could only think that his own tonsorial condition befitted an institution founded by a monk. Replying, M. de Burgh Daly welcomed members and their guests and paid tribute to the help and cooperation he had received from Miss N Clotworthy and Mr DC Moore in arranging the meeting, and to Mr Michael Perrin, Treasurer of the Hospital and chairman of the Board of Governors, for permission to use the Great Hall. He recalled that until recently, the floor of the hall had been so affected by dry rot that the number of people present had to be limited and these uniformly spread throughout the Hall – circumstances, which would have made dinner a somewhat awkward affair, but happily were now unnecessary. HP Gilding then rose to remind The Society that one of their Honorary Members, F Peyton Rous, had recently been awarded the Nobel Prize in Medicine for his work in experimental pathology, and that this brought the number of present members of The Society who were Prize winners to 14*. He proposed that the Secretaries should send a letter of congratulation to Peyton Rous. This proposal was passed by acclamation.

On Saturday, beginning at 10 am with JP Quilliam in the chair meeting ended, a further ten papers were taken before lunch at 12:30, and in the afternoon, under the chairmanship of N Joels, the remaining six were heard. The meeting ended earlier than scheduled at 3:30, but the day was saved by the provision of tea.

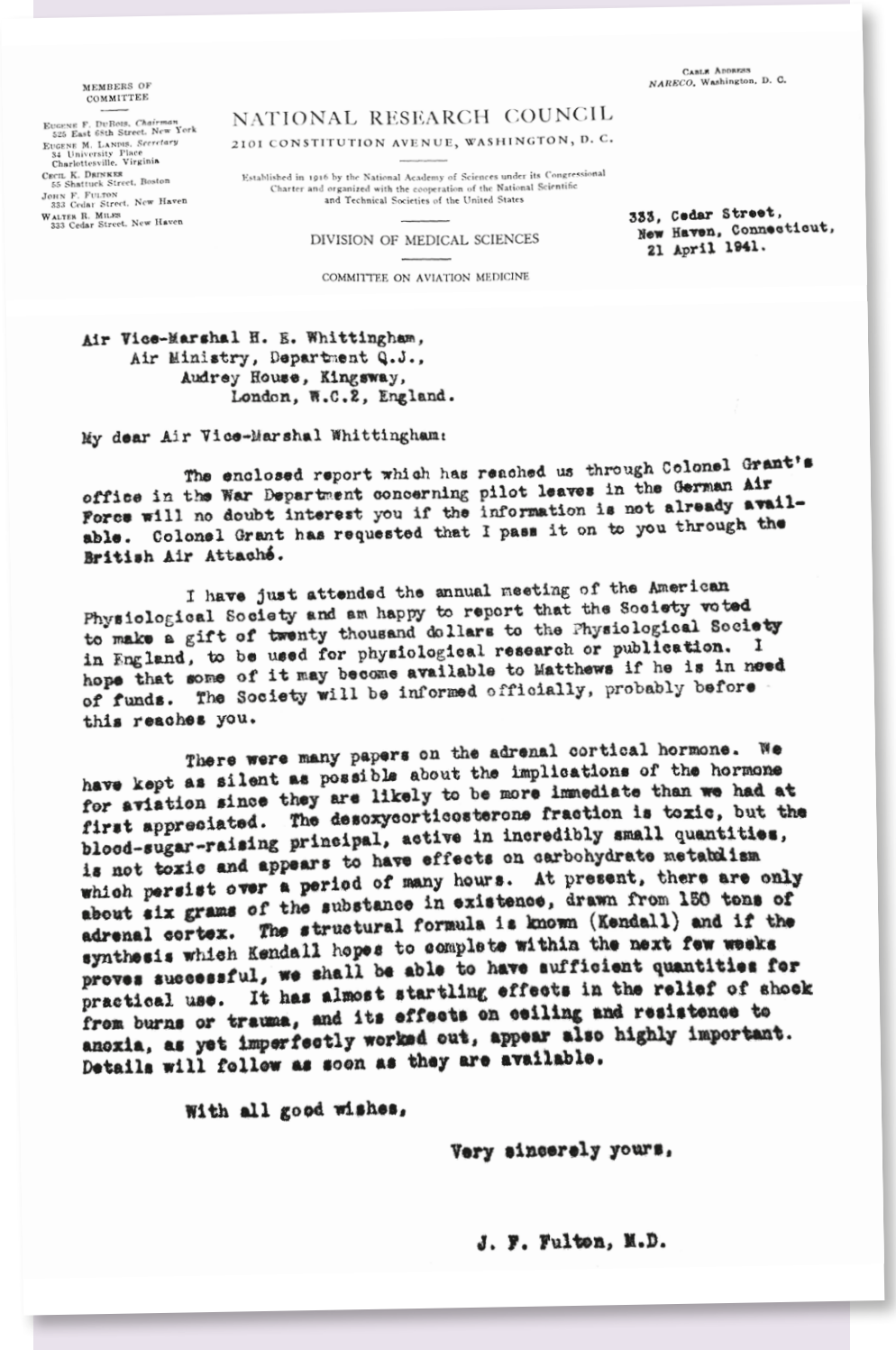
Friday 16 December: Tea 189, Dinner 112,

Saturday 17 December: Coffee 80, Lunch 114, Tea 114

*The Nobel laureates are: Lord Adrian, Professor CH Best, Sir Henry Dale Professor, Sir John Eccles, Lord Plorey, Professor C Heymans, Professor Hess, Professor AV Hill, Professor AL Hodgkin, Professor AFHuxley, Professor BA Houssay, Professor Sir Hans Krebs, Sir Peter Medawar, Dr F Peyton Rous.

From the archives of the US National Academy of Sciences, found by Jay Dean

Martin Frank of the America Physiological Society reported to Casey Early that a member, Jay Dean of the University of South Florida, Tampa, recently visited the archives at the National Academy of Sciences and came across the letter reproduced below. This indicates that APS gave The Physiological Society $20,000 for research and publications. He added 'Should you decide to pay us back, the $20,000 is equivalent to $335,000 in current dollars'.



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DIVISION OF MEDICAL SCIENCES

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Cable Address
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333, Cedar Street,
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21 April 1941.

Air Vice-Marshal H. E. Whittingham,
Air Ministry, Department Q.J.,
Audrey House, Kingsway,
London, W.C.2, England.

My dear Air Vice-Marshal Whittingham:

The enclosed report which has reached us through Colonel Grant's office in the War Department concerning pilot leaves in the German Air Force will no doubt interest you if the information is not already available. Colonel Grant has requested that I pass it on to you through the British Air Attaché.

I have just attended the annual meeting of the American Physiological Society and am happy to report that the Society voted to make a gift of twenty thousand dollars to the Physiological Society in England, to be used for physiological research or publication. I hope that some of it may become available to Matthews if he is in need of funds. The Society will be informed officially, probably before this reaches you.

There were many papers on the adrenal cortical hormone. We have kept as silent as possible about the implications of the hormone for aviation since they are likely to be more immediate than we had at first appreciated. The desoxycorticosterone fraction is toxic, but the blood-sugar-raising principal, active in incredibly small quantities, is not toxic and appears to have effects on carbohydrate metabolism which persist over a period of many hours. At present, there are only about six grams of the substance in existence, drawn from 150 tons of adrenal cortex. The structural formula is known (Kendall) and if the synthesis which Kendall hopes to complete within the next few weeks proves successful, we shall be able to have sufficient quantities for practical use. It has almost startling effects in the relief of shock from burns or trauma, and its effects on ceiling and resistence to anoxia, as yet imperfectly worked out, appear also highly important. Details will follow as soon as they are available.

With all good wishes,

Very sincerely yours,

J. F. Fulton, M.D.

Non-invasive imaging of transient biomolecular machines *in vivo*

Adam talks about his work in the Molecular Medicine Lab, which aims to develop new chemical tools to monitor and modulate effectors of disease

Adam Shuhendler

Assistant Professor, Department of Chemistry and Biomedical Science, University of Ottawa

While homeostasis is considered a steady state in physiology, it is by no means static. Instead, it is the sum of a concerted effect of sub-cellular events driven by molecular machines. These machines range from large enzymes to reactive small molecules, all of which exert an effect on the cell to alter its function for better or for worse.

Indeed, the over- or under-activity of these molecular machines can result in disease or injury (e.g. reactive oxygen species (ROS) and inflammation), or in an intended response to applied therapy (e.g. tumor casapase-3 (apoptosis) activation following radiation or chemotherapy). These active biomolecules rarely work in isolation, but are rather parts of integral networks within which any single sub-cellular machine is only transiently active or transiently present, often rapidly giving way to its successor in the signaling chain. This transiency makes these biomolecular machines elusive to analysis by traditional *ex vivo* methods in the context of the living organism.

However, measuring the activity of these molecules and overcoming the difficulty of target transiency can enable both the detection of disease prior to outward signs and symptoms, and the assessment of the success or failure of therapy prior to disease progression (Aboagye, 2006; Aboagye, 2010). Molecular imaging is a powerful tool for assessing a target biomolecular machine non-invasively and longitudinally over an entire volume of interest in living subjects (James & Gambhir, 2012). The ability to apply molecular imaging to interrogate these highly transient sub-cellular functions of fundamental importance in living subjects is provided by new chemistries for the design of activatable molecular imaging probes over a range of pre-clinical (i.e. fluorescent) to clinically-relevant (PET, MRI) imaging modalities.

Reactive oxygen species (ROS) are highly reactive oxygen-centered biomolecules underlying a broad range of diseases (Winterbourn, 2008). In the context of injury, ROS are very early effectors of the tissue response to the source of harm. Novel optical nanoprobes have been developed from semiconducting polymers that can sensitively report on the presence of specific ROS in living mice (Pu *et al.*, 2013; Pu *et al.*, 2014; Shuhendler *et al.*, 2014). Our work with the nanoprobes has enabled the real-time detection of the very early response of tissues to mechanical or chemical injury in real-time and in living subjects.

The very early response to tissue injury (i.e. within the first 30 min) have been imaged with evidence pointing to the mast cell component of the innate immune system as being responsible for the very early ROS signaling (Fig. 1; previously unpublished data). Additionally, a dual optical channel probe has been developed capable of the real-time differentiation of hydrogen peroxide *versus* peroxynitrite mediated drug-induced hepatotoxicity in living subjects (Shuhendler *et al.*, 2014).

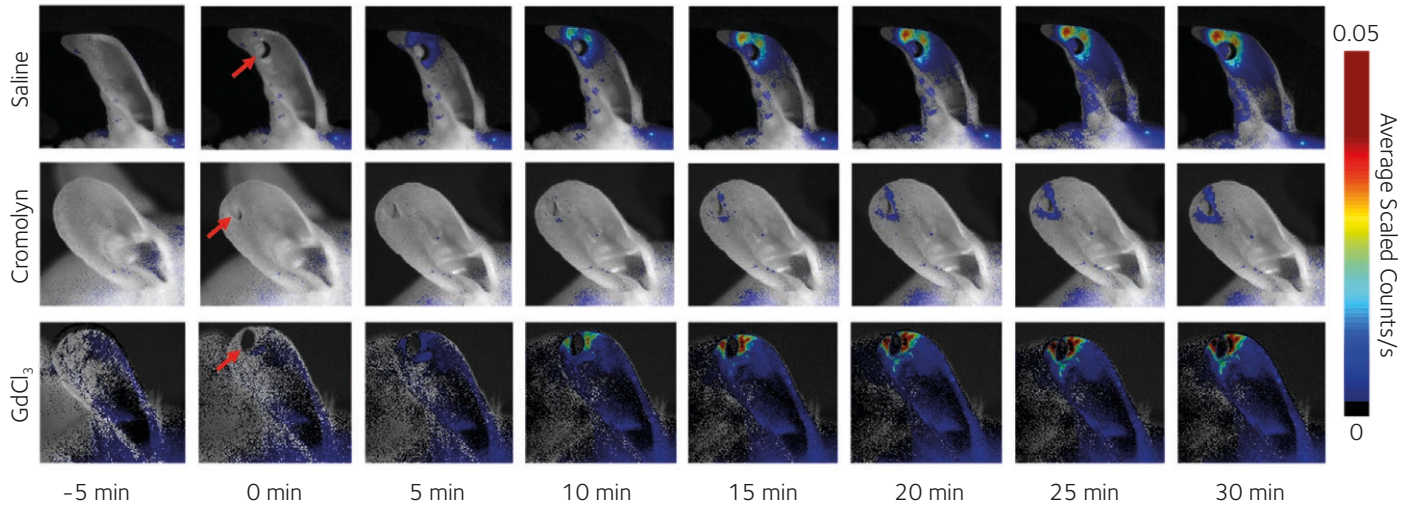
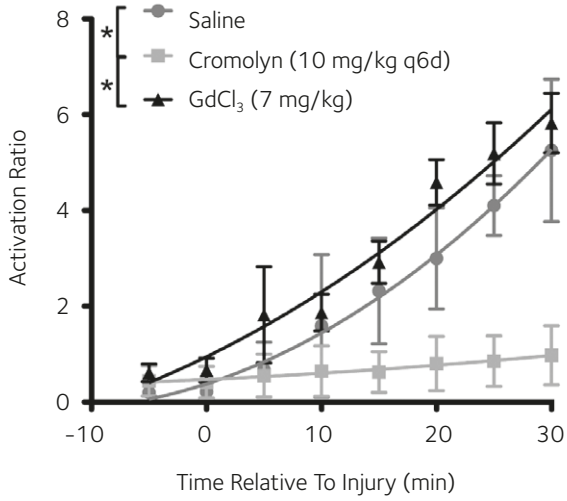
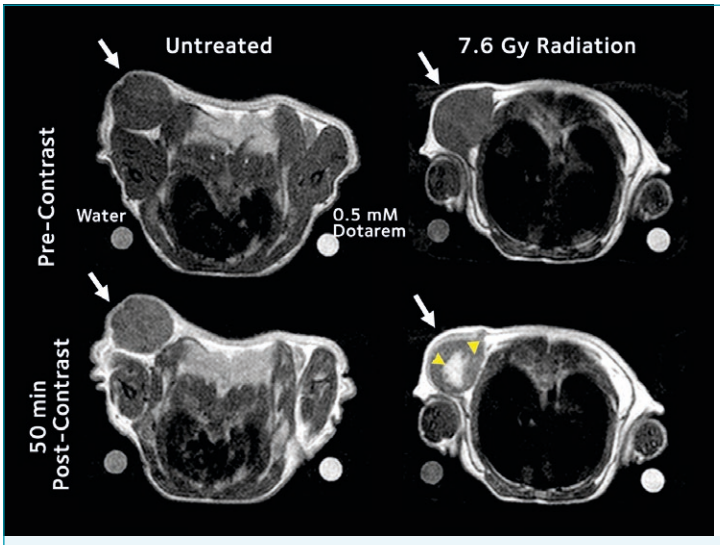


Figure 1. Real-time imaging of the evolution of reactive oxygen species (ROS) due to sterile injury to mouse pina. Mice were administered vehicle (saline), 10 mg/kg cromolyn, an inhibitor of mast cell degranulation, every day for 6 days (cromolyn), or 7 mg/kg gadolinium chloride ($GdCl_3$) to inhibit macrophage activation. Nanoprobe was administered intravenously 5 min prior to induction of sterile injury to mouse pina, and images were acquired every 5 min for half an hour. A significant reduction in ROS production was observed (*p<0.05 by general linear model repeated measures analysis) with cromolyn treatment only, suggesting mast cell involvement in early tissue response to sterile injury.





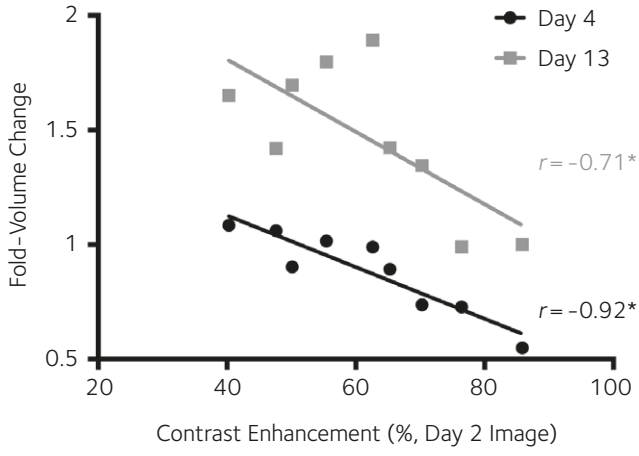


Figure 2. Predicting the response of tumor-bearing mice to radiation therapy by imaging caspase-3 activity with a macrocyclization probe. Left: Representative MR images of untreated (left) and treated mice (right) pre- (top) and 50 min post-injection of macrocylization contrast agent (bottom). Tumor is indicated by white arrow, apoptosis is indicated by yellow arrowhead. Water and 0.5 mM Dotarem phantoms are shown on bottom left and right, respectively, of each image. Right: Tumor size change was measured as the fold-change in volume 4 days (black circles) or 13 days (red square) following treatment, and correlated to MR signal enhancement measured 2 days following treatment. Pearson's correlation coefficients (r) are shown for day 4 and day 13 following treatment (* p<0.05). Adapted from Scientific Reports (2015) 5:14759.

‘The molecular imaging of these key sub-cellular machines is sure to continue to provide an unprecedented level of interrogation of physiology to both enhance our investigations of health and disease, and improve clinical outcomes’

Caspase-3 is a cysteine-aspartate protease whose activation signals the committal of the cell to die through apoptosis, a common death pathway induced by a variety of cancer chemotherapeutics and radiation. We designed a modular probe to undergo bioorthogonal macrocyclization upon activation by caspase-3, with the macrocycles self-assembling into nanoparticles *in situ* in tumor tissue (Shen *et al.*, 2013; Shuhendler *et al.*, 2015; Ye *et al.*, 2014a; Ye *et al.*, 2014b). Since caspase-3 activity correlated with the degree of probe retention in dying tumor tissue, this molecular imaging strategy was applicable to imaging through fluorescence, PET, and MRI. Importantly, this self-assembling molecular imaging probe was able to predict the degree of therapy outcome (i.e. the degree of tumor treatment effect) in mice following a single imaging session 48 hours after a single dose of therapy (Fig. 2).

Enhanced contrast production following therapy was not detected using a non-activatable control analog, illustrating the utility of our bioorthogonal self-assembly probe design for therapy response monitoring. Multiple sub-cellular markers for apoptosis have been identified each with molecular imaging probes targeting these sub-cellular changes, including annexin-V detecting phosphatidyl serine flipping from the inner to the outer cell membrane, ML-10 detecting depolarization of the cellular membrane, and fluorodeoxyglucose detecting the loss of metabolic function (i.e. reduced glucose utilization) (Witney *et al.*, 2015). When these targets and respective probes were compared to the macrocyclization probe responding to caspase-3 activation, only the macrocyclizing probe accurately reported tumor response to therapy in living subjects as confirmed by *ex vivo* measurement of apoptosis (Witney *et al.*, 2015). The ability of the macrocyclization agent to directly probe the effector of apoptotic cell death (i.e. caspase-3) and to significantly amplify the enzyme activity signal by being a substrate of this molecular machine may account for its performance *in vivo*.

The ability to investigate transient biomolecular machines in living subjects by molecular imaging can provide non-invasive, longitudinal, and predictive data about sub-cellular physiology within the intact organism. The molecular imaging of these key sub-cellular machines is sure to continue to provide an unprecedented level of interrogation of physiology to both enhance our investigations of health and disease, and improve clinical outcomes.

References

Aboagye EO (2006). Imaging in drug development. *Clin Adv Hematol Oncol* **4**, 902–904

Aboagye EO (2010). The future of imaging: developing the tools for monitoring response to therapy in oncology: the 2009 Sir James MacKenzie Davidson Memorial lecture. *Br J Radiol* **83**, 814–822

James ML & Gambhir SS (2012). A molecular imaging primer: modalities, imaging agents, and applications. *Physiol Rev* **92**, 897–965

Pu K, Shuhendler AJ, Jokerst JV, Mei J, Gambhir SS, Bao Z & Rao J (2014). Semiconducting polymer nanoparticles as photoacoustic molecular imaging probes in living mice. *Nat Nanotechnol* **9**, 233–239

Pu K, Shuhendler AJ & Rao J (2013). Semiconducting polymer nanoprobe for in vivo imaging of reactive oxygen and nitrogen species. *Angew Chem Int Ed Engl* **52**, 10325–10329

Shen B, Jeon J, Palner M, Ye D, Shuhendler A, Chin FT & Rao J (2013). Positron emission tomography imaging of drug-induced tumor apoptosis with a caspase-triggered nanoaggregation probe. *Angew Chem Int Ed Engl* **52**, 10511–10514

Shuhendler AJ, Pu K, Cui L, Uetrecht JP & Rao J (2014). Real-time imaging of oxidative and nitrosative stress in the liver of live animals for drug-toxicity testing. *Nat Biotechnol* **32**, 373–380

Shuhendler AJ, Ye D, Brewer KD, Bazalova-Carter M, Lee KH, Kempen P, Dane Wittrup K, Graves EE, Rutt B & Rao J (2015). Molecular Magnetic Resonance Imaging of Tumor Response to Therapy. *Sci Rep* **5**, 14759

Winterbourn CC (2008). Reconciling the chemistry and biology of reactive oxygen species. *Nat Chem Biol* **4**, 278–286

Witney TH, Hoehne A, Reeves RE, Ilovich O, Namavari M, Shen B, Chin FT, Rao J & Gambhir SS (2015). A Systematic Comparison of 18F-C-SNAT to Established Radiotracer Imaging Agents for the Detection of Tumor Response to Treatment. *Clin Cancer Res* **21**, 3896–3905

Ye D, Shuhendler AJ, Cui L, Tong L, Tee SS, Tikhomirov G, Felsher DW & Rao J (2014a). Bioorthogonal cyclization-mediated in situ self-assembly of small-molecule probes for imaging caspase activity in vivo. *Nat Chem* **6**, 519–526

Ye D, Shuhendler AJ, Pandit P, Brewer KD, Tee SS, Cui L, Tikhomirov G, Rutt B & Rao J (2014b). Caspase-responsive smart gadolinium-based contrast agent for magnetic resonance imaging of drug-induced apoptosis. *Chem Sci* **4**, 3845–3852

Imaging Molecular Dynamics for Drug Discovery

In the fight against cancer, Kurt Anderson and his collaborators are using advanced imaging to characterise drug response

Max Nobis, David Herrmann & Paul Timpson

Garvan Institute for Medical Research, Sydney, Australia

Zahra Erami

Albert Einstein College of Medicine, New York, USA

Ewan McGhee

Beatson Institute for Cancer Research, Glasgow, UK

Kurt Anderson

The Francis Crick Institute, London, UK

Since the discovery of the green fluorescent protein (GFP) in the early 1990s, the properties of fluorescent proteins have been greatly improved through genetic manipulation of the tri-peptide chromophore at the heart of the protein. Early improvements led to probes which were more monomeric, brighter, more photo-stable, and had a broader spectral range (reviewed in Muller-Taubenberger & Anderson, 2007).

Fluorescent proteins have been used in a variety of approaches to develop biosensors, which use fluorescence to read out the activation status of cellular signalling pathways. In the simplest case, knocking an FP into an endogenous gene locus can be used as a reporter of gene expression. FPs can also be coupled to transcription factors such as NF-κB, which translocates in and out of the nucleus in response to upstream signals such as TNFα (Nelson *et al.*, 2004). Photo-bleaching of FPs can be used to report and quantify the dynamics of structural proteins such as E-cadherin (Erami *et al.*, 2015). Finally, FPs can be used to detect conformational changes within proteins on the basis of Fluorescence Resonance Energy Transfer (FRET).

FRET is the non-radiative transfer of energy between two fluorophores having overlapping emission and excitation spectra, the proper orientation, and proximity of approximately 3 – 5 nm. Such probes can reveal unexpected feedback mechanisms by which cancer cells evade therapeutic treatment (Hirata *et al.*, 2015). FRET can be most accurately detected as a shortening of the fluorescence lifetime of the donor fluorophore. Recently, even this property has been targeted for optimisation, resulting in FPs having very long fluorescence lifetimes in order to expand the dynamic range of FRET-based biosensors (Goedhart *et al.*, 2012). Alternatively, dark acceptor FPs have been engineered which are able to accept energy from a FRET donor without themselves emitting light (Ganesan *et al.*, 2006; Pettikiriarachchi *et al.*, 2012). Such fluorophores facilitate the multiplexing of FRET probes to read out the states of multiple signal transduction pathways simultaneously, which is increasingly important for understanding the responses of complex biological systems (Machacek *et al.*, 2009).

The cost of developing a new drug doubles approximately every 9 years (Nosengo, 2016). This crisis in drug discovery requires innovative new approaches at all stages of the discovery pipeline, but especially at the later stages when failure becomes expensive. Modern high-throughput screening approaches are effective at identifying compounds, which elicit a specific cellular response in cells grown on glass coverslips. Such screens typically rely on single read-out biomarkers, although newer approaches may rely on multi-parametric phenotypic readouts such as morphology, migration, and cell cycle progression (reviewed in Conway *et al.*, 2014).

‘There has been great recent progress in the use of pre-clinical models together with advanced imaging methods to quantify where and when drugs hit their targets’

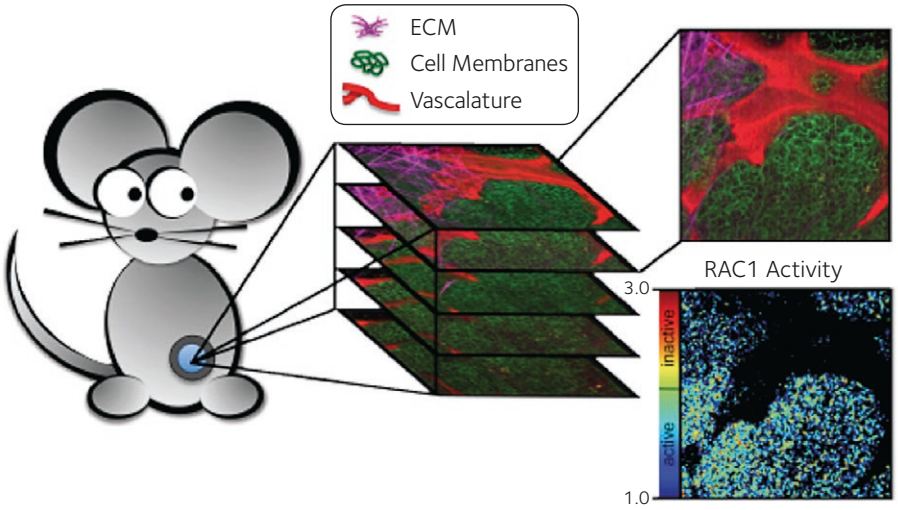


Figure 1. Intravital microscopy provides an opportunity to observe cancer progression and response to therapy in the native microenvironmental context of the disease. Label-free approaches such as second harmonic generation can be used to visualise collagen fibres of the extra-cellular matrix (ECM). The local vasculature can be visualised through the intravenous injection of fluorophores such as TRITC-labelled dextran. These methods provide contextual information needed to interpret the response of dynamic biosensors such as the Rac-Raichu probe. By using abdominal imaging windows it is possible to monitor response to therapy in the same animal over time.

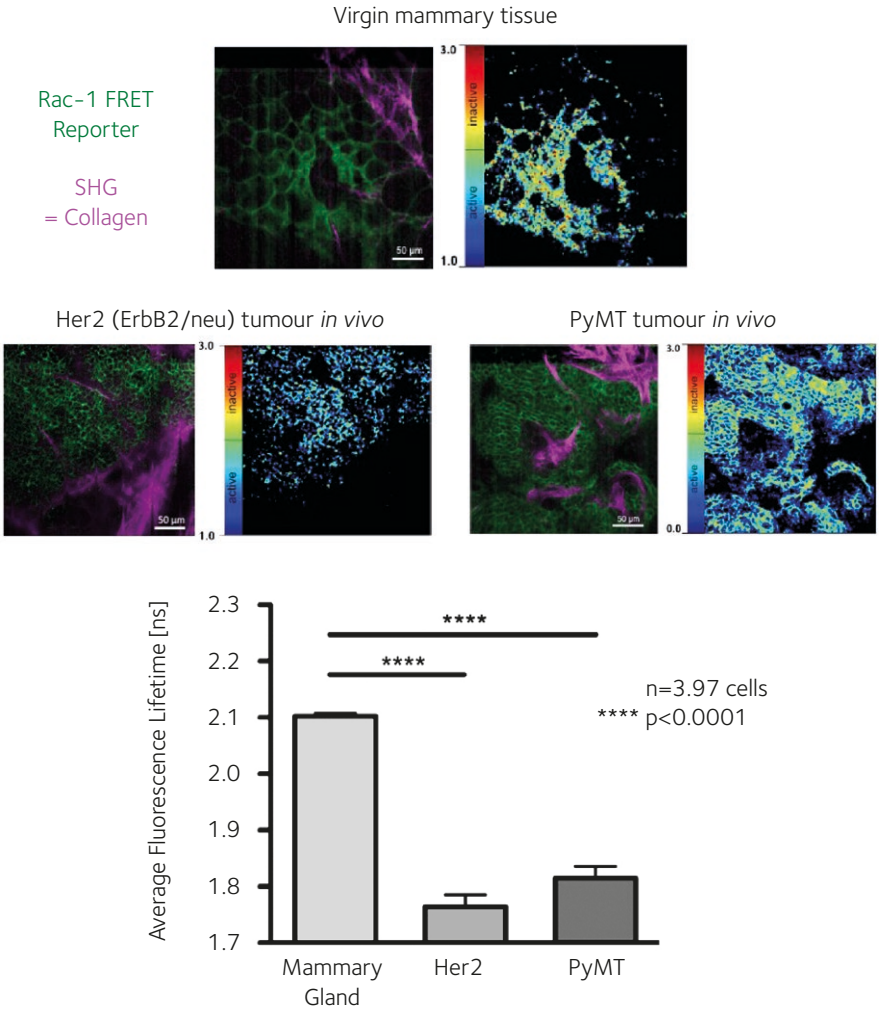


Figure 2. Rac-1 in Breast Cancer.

Unfortunately, there is a high attrition rate for progression of drug candidates from cell-based assays into the later stages of pre-clinical validation and clinical studies. We therefore urgently need better disease models on which to base predictions of clinical efficacy, and better tools with which to interrogate therapeutic response within these pre-clinical models. FRET-based biosensors have proven to be useful for cell-based assays, and more recently have been introduced into pre-clinical cancer models to facilitate the investigation of the spatial and temporal dynamics of drug action in unprecedented detail. This approach has benefitted from improvements in the design and use of surgically implanted imaging windows, which facilitate longitudinal studies in which the same animal is imaged over time. This approach improves the quality of data by reducing biological noise and thereby reduces the number of animals required to obtain a time course (eg of drug response), both of which are important aspects of the 3Rs (Burden *et al.,* 2015). Previous imaging windows were commonly restricted to use on the skin flap of nude mice (Lehr *et al.,* 1993), but recently chambers have been designed which are well tolerated over long periods of time and enable the imaging of subcutaneous organs such as breast and intra-peritoneal organs such as liver, intestine, and pancreas (Ritsma *et al.,* 2013).

There has been great recent progress in the use of pre-clinical models together with advanced imaging methods to quantify where and when drugs hit their targets. This work depends on the use of a pipeline of complementary model systems, including cultured cells, 3D culture models, organoids, *ex vivo* tissue, transplantation models, and full genetic models of disease (reviewed in (Timpson *et al.,* 2011).

In a pioneering study we used FRAP to show that the dynamics of E-cadherin in cell-cell junctions were different for the same cancer cells grown *in vitro* on glass coverslips and *in vivo* as subcutaneous tumors (Serrels *et al.,* 2009). Crucially, the response of E-cadherin to drug treatment was completely different in the two different cellular environments. In another approach, we have shown that FLIM-FRET is sufficiently sensitive to detect sub-cellular responses to drug treatment *in vivo*. Treatment of mice bearing subcutaneous PDAC tumours, with a dose of Dasatinib sufficient to inhibit PDAC metastasis, specifically inhibited Rho GTPase in the tips of cells rather than globally throughout the cell body (Timpson *et al.,* 2011). Additional work has shown that intra-vital FLIM-FRET can be used to characterise drug response in different regions of subcut PDAC tumours, and with respect to the tumour vasculature (Nobis *et al.,* 2013).

Now, our work using FRAP of E-cadherin has come full-circle with the production of a mouse expressing GFP-E-cadherin from the *Hprt* locus. This mouse enables the visualization of E-cadherin dynamics in a wide variety of tissues including liver, breast, kidney and pancreas, and has been crossed into the KPC model of pancreatic cancer to demonstrate the specific mobilization of E-cadherin in primary PDAC tumours in response to mutant p53 (Erami *et al.,* 2016). Thus, there is an emerging body of work, which clearly demonstrates the importance for drug discovery of imaging molecular dynamics in pre-clinical models.

References

Muller-Taubenberger A. & Anderson KI (2007). Recent advances using green and red fluorescent protein variants. *Appl Microbiol Biotechnol* **77**, 1-12

Nelson DE *et al.,* (2004). Oscillations in NF-kappaB signaling control the dynamics of gene expression. *Science* **306**, 704-708

Erami Z, Timpson P, Yao W, Zaidel-Bar R & Anderson KI (2015). There are four dynamically and functionally distinct populations of E-cadherin in cell junctions. *Biol Open* **4**, 1481-1489

Hirata E *et al.,* (2015). Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin beta1/FAK signaling. *Cancer Cell* **27**, 574-588

Goedhart J *et al.,* (2012). Structure-guided evolution of cyan fluorescent proteins towards a quantum yield of 93%. *Nat Commun* **3**, 751

Ganesan S, Ameer-Beg SM, Ng TT, Vojnovic B & Wouters FSA (2006). Dark yellow fluorescent protein (YFP)-based Resonance Energy-Accepting Chromoprotein (REACh) for Forster resonance energy transfer with GFP. *Proc Natl Acad Sci U S A* **103**, 4089-4094

Pettikiriarachchi A, Gong L, Perugini MA, Devenish RJ & Prescott M (2012).Ultramarine, a chromoprotein acceptor for Forster resonance energy transfer. *PLoS One* **7**, e41028

Machacek M *et al.,* (2009). Coordination of Rho GTPase activities during cell protrusion. *Nature* **461**, 99-103

Nosengo N (2016). Can you teach old drugs new tricks? *Nature* **534**, 314-316

Conway JR, Carragher NO & Timpson P (2014). Developments in preclinical cancer imaging: innovating the discovery of therapeutics. *Nat Rev Cancer* **14**, 314-328

Burden N, Chapman K, Sewell F & Robinson V (2015). Pioneering better science through the 3Rs: an introduction to the national centre for the replacement, refinement, and reduction of animals in research (NC3Rs). *J Am Assoc Lab Anim Sci* **54**, 198-208

Lehr HA, Leunig M, Menger MD, Nolte D & Messmer K (1993). Dorsal skinfold chamber technique for intravital microscopy in nude mice. *Am J Pathol* **143**, 1055-1062

Ritsma L *et al.,* (2013). Surgical implantation of an abdominal imaging window for intravital microscopy. *Nat Protoc* **8**, 583-594

Timpson P, McGhee EJ & Anderson KI (2011) Imaging molecular dynamics in vivo - from cell biology to animal models. *J Cell Sci* **124**, 2877-2890

Serrels A. *et al.,* (2009). Real-time study of E-cadherin and membrane dynamics in living animals: implications for disease modeling and drug development. *Cancer research* **69**, 2714-2719

Timpson P. *et al.,* (2011). Spatial regulation of RhoA activity during pancreatic cancer cell invasion driven by mutant p53. *Cancer research* **71**, 747-757

Nobis, M. *et al.,* (2013). Intravital FLIM-FRET imaging reveals dasatinib-induced spatial control of src in pancreatic cancer. *Cancer research* **73**, 4674-4686

Erami, Z. *et al.* (2016). Intravital FRAP Imaging using an E-cadherin-GFP Mouse Reveals Disease- and Drug-Dependent Dynamic Regulation of Cell-Cell Junctions in Live Tissue. *Cell Rep* **14**, 152-167

Imaging tumour biochemistry *in vivo*

Developing next generation tools for cancer diagnosis, monitoring of therapeutic response and detection of drug resistance

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Advances in modern-day medicine and the associated increase in life-span has resulted in an increased prevalence of age-related diseases, such as cancer. Despite substantial funding and some exciting breakthroughs, we are still a long way from turning this debilitating disease into a chronic illness. In many cases, we lack the tools to detect the disease at an early stage, where patients are most likely to respond to therapy. Moreover, in the clinic there is still a long way to go before the realisation of precision medicine, where patients receive the drug that is tailored to their individual disease. Through the development of advanced imaging techniques we aim to make precision medicine a reality.

My group is interested in creating new imaging agents and techniques to understand cancer growth, development and cell death. Imaging provides the ability to study these processes in living organisms with unrivalled temporal and spatial resolution, without the need for invasive biopsy sampling. With imaging, we are not limited to studying a snap-shot of a small section from the primary tumour, but can interrogate the cancer in its entirety, including tumours that may have metastasised to distant regions in the body. Importantly, we can study these processes in people and not just in animal models of cancer. This is enormously powerful and is what gets me so excited about being in this field.

As a biochemist by training, I've always been particularly interested in how cancer cells alter the way they consume nutrients in order to grow at such a rapid pace and outcompete surrounding normal tissue. Through the development of novel imaging tools, we can probe cancer biochemistry in living organisms. In hospitals throughout the world, cancer is routinely detected and monitored using a radioactive version of glucose, known as fluorodeoxyglucose, or FDG for short. Using an imaging method known as positron emission tomography (PET), we can map in 3D where the radioactive glucose is in the body. Tumours take up a lot of glucose in order to maintain their highly proliferative state, and so 'light up' in the PET scan. Using other radiolabelled molecules, we have been able to look not only at glucose utilisation, but explore how tumour cells use lipids as an alternative energy source, store glucose for a rainy day as glycogen, and probe the activity of key enzymes that regulate these processes.

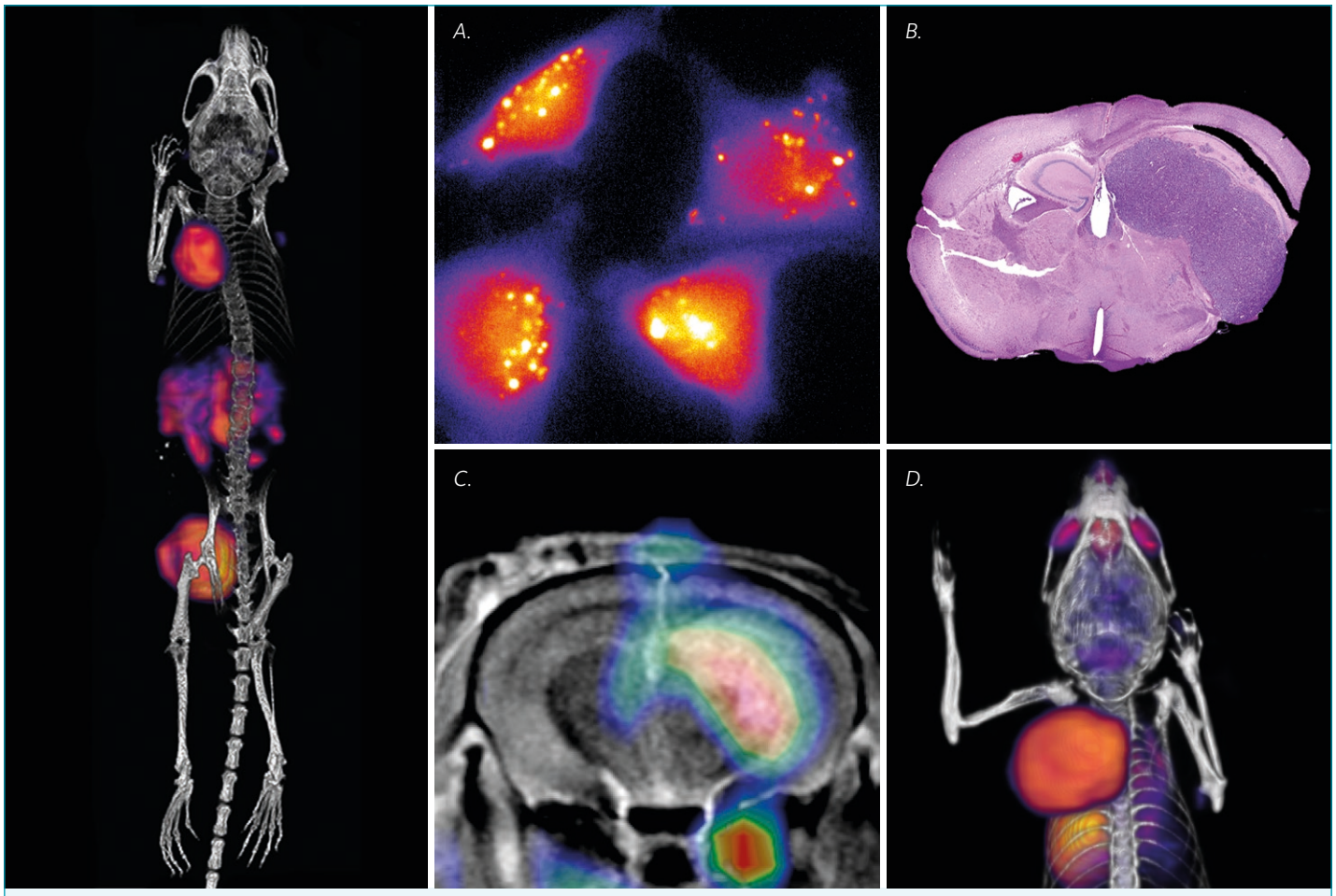

Figure 1. We are developing novel imaging tools to detect molecular processes in cancer, from the cellular and tissue, to whole-body level, using positron emission tomography. *A.* Imaging glucose storage as glycogen in single ovarian cancer cells using fluorescence microscopy. Single glycogen granules can be resolved. *B.* Histological section of a mouse brain containing an orthotopically-implanted human brain tumour. *C.* Non-invasive detection of the same brain tumour through the measurement of tumour-specific metabolic processes with positron emission tomography. The tumour 'lights up' in the colour image. Another imaging technique, magnetic resonance imaging (in greyscale), is used to show anatomical features. *D.* Imaging of glucose uptake in 3D using positron emission tomography. A glucose-avid tumour is located on the left shoulder of the mouse.

More recently, my research has shifted to focus on the pressing issue of drug resistance in cancer. Resistance to chemotherapy and molecularly-targeted therapies provides a major hurdle for cancer treatment, due to the underlying genetic and biochemical heterogeneity of tumours. Despite intensive research, the field has struggled to provide a solution for sensitive and specific molecular imaging of tumour response and resistance to therapy. We are looking at methods that cancer cells employ to resist traditional therapies, such as altered metabolism, and are actively pursuing these biomarkers as potential targets for imaging. A new diagnostic imaging test that can predict drug resistance will enable patient stratification, enabling the clinician to select an alternate therapy for the individual patient using a precision medicine approach. Where no suitable treatment options are available, patients with resistant disease will no longer receive inappropriate second-line treatment, thus avoiding associated side effects; resulting in substantially improved quality of life and the opportunity to initiate palliative care at an earlier stage.

Imaging probe development is an expensive process, requiring a multidisciplinary approach that spans the disciplines of the biomedical and physical sciences. I am lucky enough to work in a Centre that lives and breathes collaborative science, and have the support of the Wellcome Trust and the Royal Society. Imaging has shown to play a vital role in patient management, but we have only scratched the surface of what can be achieved. It is my hope that the next generation of imaging tools and techniques will lead to a better understanding of cancer and how we can keep it at bay.

Tim is a Group Leader in the Centre for Advanced Biomedical Imaging (CABI) at University College London (UCL), Wellcome Trust/Royal Society Sir Henry Dale Fellow and UCL Excellence Fellow.

'Tumours take up a lot of glucose in order to maintain their highly proliferative state, and so 'light up' in the PET scan'

It was the best of times – a postdoctoral experience in the UK in the 1960s

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In August 1966, my wife, Ellen, our two young children and I boarded the Nieuw Amsterdam in the former New Amsterdam, bound for the next stage of our lives: we were moving to Cambridge, England. I had just completed 3 years of Vietnam era military service voltage clamping lobster axons at the Naval Medical Research Institute (Bethesda, Maryland), and had received an NIH Special Fellowship to work in Alan Hodgkin's laboratory. My first exposure to Cambridge dons, aside from a brief meeting with Alan a year earlier, was William Rushton, a fellow passenger on the Nieuw Amsterdam, who had been one of Alan's mentors, and whose work was well known to me. This, of course, was the reason I was headed to Cambridge: to learn from the pioneers of cellular neurophysiology. In preparation for this experience, I had read Muriel Beadle (*These Ruins are Inhabited*), CP Snow (*The Masters* etc.) and GM Trevelyan (*History of England*), as well as key nerve and muscle physiology papers from the Cambridge luminaries. I was also steeped in Cambridge lore from my Washington University Medical School mentors, Daniel Tosteson and Paul Horowicz, and from W Knox Chandler, who was completing his fellowship in Hodgkin's laboratory.

As stated in my fellowship application, my plan was to spend the Autumn squid season at the marine laboratory in Plymouth (Fig. 1), to elucidate further details of ionic conductances with voltage clamped squid axons. Upon arrival in Cambridge, however, I learned that Peter Baker, Alan's young protégé, would lead the Cambridge contingent to Plymouth, and that he wanted 'all hands to the (sodium) pump'. I was not totally unhappy with the change of plans, but it became a career changer. I had already mastered several research methodologies, beginning as a Cornell undergraduate studying insect metamorphosis with Howard Schneiderman, who revered Cambridge zoologist, VB Wigglesworth. At Cornell I was also introduced to H & H and the action potential by William Van der Kloot. As a medical student I worked on the Na/K-ATPase with Tosteson. During my Navy service, I learned voltage clamping from David Goldman and a brief stint at Woods Hole with John Moore and Toshio Narahashi. My main objective in going to Cambridge was to learn more about analyzing scientific questions: what are the thought processes that distinguish elite investigators? I was not to be disappointed.

Even though it was 21 years post-WW II, the UK was still feeling much more austerity than the US (the Pound, Sterling was devalued during our stay). Thus, one of the first lessons I learned was to plan experiments really carefully to conserve resources and curtail costs (and save time).

Serendipity

My first thrilling experience occurred just about 3 weeks into my fellowship. Richard (Rick) Steinhardt, Richard Keynes' postdoctoral fellow and my Plymouth lab mate, and I discovered a large Na^+ efflux from squid axons when Na^+ was removed from the artificial sea water (asw) bathing the axons. This Na^+ efflux was not inhibited by ouabain or K^+-free asw and, thus, was not Na^+ pump-mediated. Peter, Rick and I reasoned that this Na^+ efflux had to be either Na^+ co-transported with an anion (likely Cl^-) or exchanged for Ca^{2+} or Mg^{2+}, the only other cations in the asw. The simplest test was to delete the Ca^{2+} and, in the first experiment, we had our answer: an external Ca^{2+}, dependent Na^+ efflux, Na/Ca exchange (NCX)! What a glorious start to my traineeship!

My next major learning experience came about a month later, when Alan came to Plymouth to see how I was getting on. Alan spent a few days modeling our Na^+ efflux data and helping dissect squid axons – he obviously greatly enjoyed both activities. The squid arrived at the lab in mid-afternoon so experiments were performed in the evening, and Rick and I would test the day's model. Invariably, we would obtain a result that didn't fit the model, but the new data would lead to a new, refined quantitative model, and a new experimental test that evening. This was a great lesson in Alan's analytical process that

The Mayflower Guest House, Citadel Road, Plymouth, the B&B where Alan and I stayed during the squid season, as it looks today. We breakfasted at a table in the bay window (shown here), looking out over Citadel Park; we were frequently the only guests, as this was the off-season. The laboratory was nestled into an angle on the far (waterfront) side of the Citadel, just a short walk through the park from the Mayflower. (Photo courtesy of Mr. Patrick Warnock, current proprietor of the Mayflower Guest House.)

has long stood me in good stead. Further, it fit his strong opinion that physiology depends critically upon hand-eye coordination and manual dexterity (i.e., the actual experiments) as well as upon the intellectual prowess to design good experiments. The only time I ever saw Alan become really upset was several years later: a competitor questioned some of his results and he rapidly retorted, '*I did the experiments, I know they're right*!'

Peter had warned me that Alan was busy with other matters and would not participate directly in my experiments. After just a few days, however, Alan asked if I would mind if he stayed in Plymouth to work with me. To say that I was thrilled would be a gross understatement! Alan obviously was excited by our discovery, and this gave me the opportunity to work directly with the 'great man,' himself. Alan and I perform the initial set of our proposed Ca^{2+} influx experiments the following week. The very first experiment revealed that the large external Ca^{2+}-dependent Na^+ efflux in Na^+-free asw was associated with a large ^{45}Ca influx, as predicted. Voila! NCX was verified! [Note: a more detailed account of the NCX discovery is given in a *PN* article that I wrote with Harald Reuter (Blaustein & Reuter, 2014), who discovered NCX in mammalian cardiac muscle at the very same time we found it in squid axons.]

Occasional weekends off for 'good behavior'

My family was living in Cambridge, where my daughter was starting primary school. Thus, during the squid season (mid-September to Christmas), I only got to see them about every third weekend. I would do an all-night experiment on Friday and then catch the early Saturday train from Plymouth to London (with a little shut-eye during the 5-hour journey). Ellen would meet me in London, and we would 'do the town' (museums, theatre, concerts, etc.), and then head to Cambridge late Saturday night or early Sunday to spend time as a family (Ellen had hired an Italian au pair, who stayed with the children during our London excursions). It was work hard-play hard! The London sites and cultural activities were an exhilarating change of pace, but no less exhausting.

On Monday mornings I'd take the early train to London so I could get back to Plymouth before the squid arrived. Not a squid day was to be wasted because Knox Chandler had regaled me about the devastating consequences of Plymouth gales – with no squid for days afterward. One fortuitous aspect of the early train ride was my almost invariable meeting with Andrew Huxley who was then Chair of the University College Physiology Department. He lived in Grantchester, and would usually take the early Monday train to London where he would spend much of the week. Andrew was very generous with his time during those trips, and I got to know him much better than might have been the case if we met only at Phys Soc meetings. Indeed, that friendship lasted until his death. Hugo Gonzales-Serratos, who was Andrew's research student in the mid 1960's, joined the Biophysics Department at the University of Maryland in 1979, at the time I became Chair of Physiology. We arranged for Andrew to visit the University of Maryland on several occasions, including once to present a named lecture. During one of my visits to Cambridge in the 1980's, I was Andrew's guest at Trinity where he was the Master. He guided me on a most memorable tour of the Wren Library and some of its greatly prized books, including Newton's own copy of the *Principia* – a special treat for a book lover and book collector (and the son of a book publisher and collector).

'As I cycled past King's College Chapel, *en route* to the Physiological Laboratory every morning, I would pinch myself to be sure that it wasn't just a fairytale'

A family affair

At the end of the 1966 squid season, in mid-December, I rejoined my family in Cambridge – and learned that my Jewish daughter had been appropriately selected to play the Virgin Mary in her school's Christmas Pageant. Alan had been so enthused about our squid results that he went back to Plymouth early in January for a few more experiments on the last of the season's squid – but he forbade me to leave my family and join him. The next January, I took my family to visit Plymouth while I completed a last few experiments for our *J Physiol* NCX and Na^+ pump papers.

While I was in Plymouth, my 'squidow' (local term for wives left behind), Ellen, was busy making new friends – especially amongst the Cambridge 'transients.' One was Marcella Ross, whose husband, Leonard, a neuroanatomist from Philadelphia, was on sabbatical. Ellen invited them to dinner, where I learned about Len's work on the structure of isolated nerve endings (synaptosomes) in Victor Whittaker's laboratory in the Biochemistry Department. I was immediately intrigued by the possibility that synaptosomes might be amenable to physiological study. Thus, at my first opportunity, I visited Len and Roger Marchbanks in their lab (Victor was away). Indeed, my first published study after returning to the States was on NCX in synaptosomes (Blaustein & Wiesmann, 1970). This was just the first of >50 studies on the physiology of synaptosomes that my trainees and I performed over the next three decades – including many published in *J Physiol*. Obviously, one of the other wonderful benefits of my UK experience was the opportunity to interact with numerous outstanding scholars – trainees as well as mentors. Frequent gatherings for afternoon tea or a pub lunch with fellow trainees such as Leroy (Roy) Costantin, Virgilio Lew and Stephen Easter, and with Richard (Lord) Adrian and Ian Glynn, as well as Peter Baker, enabled us to test new ideas on a very critical audience. I rapidly learned, however, that a half-pint of bitters was my limit at the pub if I wanted to do any work in the afternoon – but bartenders often mistook my American English 'half' for 'have,' and served a full pint. My friendship with Roy led to his recruitment to the Washington University (St. Louis) Medical School Physiology & Biophysics Department, where we were colleagues until his untimely death.

Work in Cambridge was a little less hectic than in Plymouth – and we didn't have to worry about a fickle squid supply. Peter was anxious to extend our NCX studies so I agreed to measure Na^+-dependent Ca^{2+} fluxes in spider crab (*Maia squinado*) nerves. The results were reported in our first NCX paper (Baker & Blaustein, 1968). The full (*J Physiol*) squid papers didn't get published until a year later, but we presented those results at meetings of the Phys Soc. I was especially nervous at my first presentation, in the Spring of 1967, because I was forewarned to beware of penetrating questions from Andrew Huxley and Bernard Katz. Their questioning turned out to be quite mild; our findings spoke for themselves.

The squid call again

I returned to Plymouth in September 1967, and Alan joined me for part of the squid season. We had planned many of the experiments beforehand, and were able to complete virtually all of the proposed NCX studies. I also finished work for our Na^+ pump paper (the original objective of the previous season). Two other Americans came to Plymouth that year – Larry Cohen (Richard Keynes' fellow) and Bertil Hille (Alan's fellow), so there were lively, broad-ranging discussions at morning coffee and afternoon tea. Also participating were more senior scientists including visitors such as Trevor Shaw and Peter Caldwell, and Eric Denton, a permanent member of the Plymouth laboratory. A seasonal highlight was a Thanksgiving feast (on Saturday, because Thursday was a squid day) for both the American and British squidders. The venue was, appropriately, not far from the 'Mayflower Steps', the site from which the Pilgrims had embarked for Plymouth, Massachusetts in 1620. As the only 'medically-qualified' attendee, it fell on me to carve the turkey in front of all – and, to the embarrassment of the (non-British) chef, I quickly discovered an unopened bag of giblets still inside the deliciously roasted bird.

Threads of life

While I was away (again), Ellen befriended our new next-door neighbors, Joy and Mani Matter. Mani, the Bern, Switzerland, Town Counsel, was studying international law. Joy, a teacher, later became Education Minister for the Canton of Bern. Mani's avocation was satirical song writing and singing in Swiss-German dialect, and he became a folk-hero. Our friendship blossomed through the spring, with evenings spent reading poetry and plays together; it continues with Joy to this day (Mani died in a tragic auto accident in 1972). That friendship also contributed to our decision to go to Bern in 1971, where I did a 'mini-sabbatical' in Harald Reuter's laboratory – another turning point in my career. Harald and I discovered NCX in mammalian arteries. That inspired my proposal that Na^+ pumps, NCX and an 'endogenous ouabain-like compound' (the 'holy spirit') contribute to the pathogenesis of hypertension (Blaustein, 1977). In turn, that led to the discovery, with John Hamlyn (my co-worker and former trainee) and our colleagues at the Upjohn company, that ouabain is, in fact, a mammalian hormone. (Coincidentally, John was a pre-teenager growing up in Plymouth

The Cambridge Physiological Laboratory in 1995, little changed since the 60s

during my traineeship days.) This latter phase of my career is, in part, summarized in two new reviews (Blaustein *et al.,* 2016; Hamlyn & Blaustein, 2016).

Cambridge/Plymouth contemporaries and mentors

I spent the Spring of 1968 writing the three *J Physiol* papers on our squid work, while also exploring other preparations in which to study NCX. Given the fine research on red cell cation transport, especially the Na^+ pump by, e.g., Glynn and Lew, and Tosteson and Joseph Hoffman), I tested human, cow, pig and even nucleated chicken erythrocytes, but came up empty-handed. A decade later, John Parker discovered NCX in dog red cells, which have no Na^+ pumps; they employ an ATP-driven Ca^{2+} pump to generate a Ca^{2+} gradient, which NCX then uses to extrude Na^+. The evolutionary pressures that led to these family differences in erythrocyte ion regulation are fascinating to contemplate.

I was not a member of a Cambridge college, but was periodically invited to lunch or dinner or to a college feast – always enjoyable occasions. One 'ordinary' dinner was particularly memorable. I had volunteered to be a subject for one of Patrick Merton's studies on the control of muscle movement and, following the experiment, he invited me to dine at Trinity. After dinner, Pat suggested that we stay for port, and he and I remained at High Table with several senior dons, in candlelight, under the glare of Henry VIII. The elder dons, each of whose age was more than the sum of Pat's (47) and mine (32), proceeded to discuss a 1946 meeting of the Cambridge Moral Science Society that they had attended with Ludwig Wittgenstein (MSC chair), Karl Popper (invited guest from LSE) and Bertrand Russell. I was enthralled (and speechless) – as was Pat – it was surreal. Only about 5 years ago, when I read 'Wittgenstein's Poker' (Edmonds & Eidinow, 2001), did I grasp the significance of this first-hand recounting. The dons had borne witness to the (in)famous brief confrontation about whether philosophy dealt with substantive problems (Popper) or mere linguistic puzzles (Wittgenstein, who brandished a fireplace poker for emphasis). Popper used Wittgenstein's waving of the poker as an example of a 'substantive philosophical problem'. When Russell asked Wittgenstein to put down the poker, he threw it down and stormed out. Only in Cambridge!

As I cycled past King's College Chapel, *en route* to the Physiological Laboratory every morning, I would pinch myself to be sure that it wasn't just a fairytale. To a bright-eyed and bushy-tailed youngster from 'the Colonies,' it was exhilarating. I was delighted to be up to the task – not only absorbing information, but contributing new ideas. The exceptional intellect of our mentors surely was a major factor, but I daresay that equally important was input and criticism from my contemporaries. It is noteworthy that all the trainees with whom I had extensive interactions at Plymouth and Cambridge (mentioned above) went on to illustrious academic careers. It was, truly, a special time and place!

References

Baker PF & Blaustein MP (1968). Sodium-dependent uptake of calcium by crab nerve. *Biochim. Biophys. Acta* **150**:167-170.

Blaustein MP (1977). Sodium ions, calcium ions, blood pressure regulation and hypertension: a reassessment and a hypothesis. *Am. J. Physiol.* **232**:C165-C173.

Blaustein MP, Chen L, Hamlyn JM, Leenen FHH, Lingrel JB, Wier WG & Zhang Z (2016). Pivotal role of a2 Na^+ pumps in cardiovascular health and disease. *J. Physiol.*

Blaustein MP & Reuter H (2014). A tale of three cities: the discovery of sodium/calcium exchange and some of its implications. *Physiol. News* **96** (Autumn 2014):32-37.

Blaustein MP & Wiesmann WP (1970). Effect of sodium ions on calcium movements in isolated synaptic nerve terminals. *Proc. Natl. Acad. Sci. USA.* **66**:664-671.

Edmonds D & Eidinow J (2001). Wittgenstein's Poker. Harper Collins Press, New York, 340 pp.

Hamlyn JM & Blaustein MP (2016). Endogenous ouabain: recent advances and controversies. *Hypertension* **68**:526-532

Our common ancestor: Henry Newell Martin (1848–1896)

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One of the Founder Members of The Physiological Society in March 1876 was Henry Newell Martin, a protégé of both Michael Foster and Thomas Henry Huxley. That same year he was appointed the first Professor of Biology at the Johns Hopkins University at Baltimore, from where he actively promoted experimental biology and physiology, he and his laboratory exerting 'a unique influence on the development of physiology in America' (Appel 1987). He was enormously influential in ensuring the survival of the embryonic *Journal of Physiology* and guaranteeing American editorial involvement. And with Henry P Bowditch and S Weir Mitchell, he initiated the foundation of the American Physiological Society (APS), which held its preliminary meeting on December 30, 1887, in New York. Martin was largely responsible for writing the first draft of the APS Constitution, and served as first secretary-treasurer of APS from the inaugural meeting until 1892.

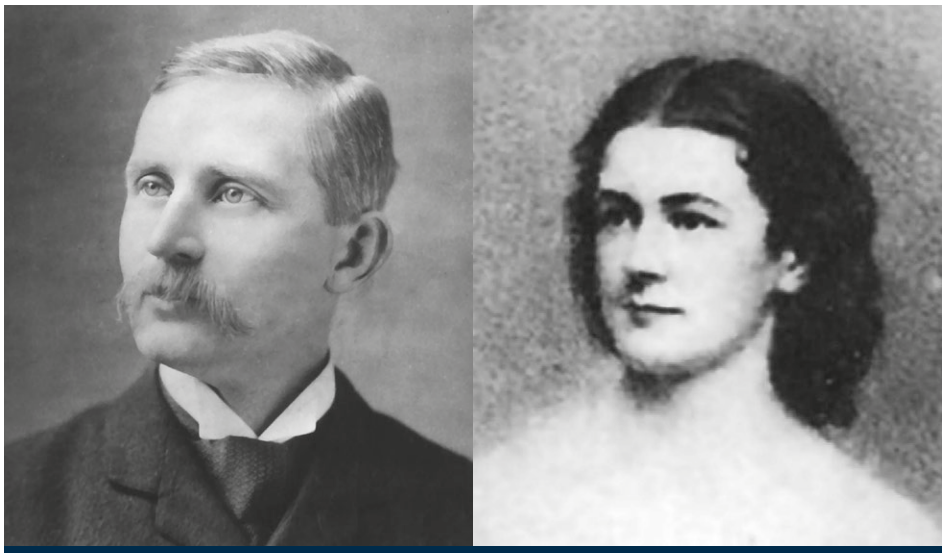
Martin, Foster and Huxley

Born in Newry, County Down in 1848, he matriculated at the University of London aged 16, where he came to the attention of Michael Foster, then working as William Sharpey's assistant at University College. He moved to Christ's College, Cambridge, in October 1870, just as Foster also moved there to become the first Praelector of Physiology at Trinity College, and in 1873 gained first place in the Natural Science Tripos at Cambridge. He assisted both Foster in Cambridge, and Huxley at the Royal College of Science, in teaching laboratory classes and in writing introductory texts (e.g. Huxley and Martin 1875). It is therefore of little surprise that when the Trustees of the new Johns Hopkins University, anxious to appoint a Professor to develop physiology research and teaching, consulted Foster and Huxley as to a suitable candidate, Martin was recommended (Sharpey-Schafer, 1927).

Martin, Johns Hopkins and *The Journal of Physiology*

Martin's immediate task in the infant Johns Hopkins University was to develop biological sciences, in preparation for the eventual creation there of a Medical School; this was the first clearly identified biological research programme in the United States (Maienschein 1987). Martin threw himself into recruiting demonstrators, students and organising classes and laboratories, often at personal

1885 photograph of Hopkins Hall, on the original downtown Baltimore campus of The Johns Hopkins University



Henry Newell Martin & Hetty Cary

expense, as Henry Sewall, later Professor of Physiology in Denver, Colorado, recalled '... my spirits were lightened when I saw a young man, he was then twenty-eight and looked younger, who treated me at once something like a companion... Martin accepted me as his assistant in the biological laboratory at a stipend of $250 for the first six months. Not for many months did I suspect that this was at first a private and not a University appointment' (Sewall 1911).

These early physiologists faced the very real problem of where to publish. In 1878, frustrated by the lack of a dedicated English-language physiological journal as opposed to general medical or anatomical journals, Michael Foster started *The Journal of Physiology* ('*The Journal*') as a private venture although clearly recognising that '*[T]he number of professional physiologists is small in both America and England; too small to support a journal taken in by physiologists only*' (Foster to Warren, mid-1878, Physiological Society Archives SA/PHY F1/3/2). He calculated that 400, preferably 500, subscribers would be necessary to support *The Journal*, which seems extraordinarily optimistic at a time when the total membership of the Physiological Society was approximately forty. Foster recruited colleagues around the world, writing to Henry Bowditch in Harvard, '*I mean to worry everyone who ought to subscribe until they do - & hope you will do the same in the States*' (Foster to Bowditch, 5.4.1878, Physiological Society Archives SA/PHY F1/3/1/9).

Financially however, the survival of *The Journal* looked shaky. In Britain, the support of the founder of the Cambridge Scientific Instrument Co., A G Dew-Smith, became essential, and in the USA during the early months of 1880, a number of American physiologists considered ways in which they could help. Martin immediately negotiated with the Johns Hopkins Trustees to provide a subsidy of $250, on condition that Foster include an agreed acknowledgment, 'published in America with the aid of the Johns Hopkin University', on the title page of *The Journal*. By the end of that year, British publication was taken over by the Cambridge Scientific Instrument Co., and Johns Hopkins University acted as *The Journal*'s American publishers and distributors, although Martin uncovered the disturbing fact that there were at that time only 12 American subscribers to *The Journal* (Martin to Bowditch, late 1880, Physiological Society Archives, SA/PHY/ F1/3/3). By the end of the century, however, it was felt that the market for physiological papers was such as to warrant a second journal in the field, and William Porter of Harvard established the *American Journal of Physiology* in 1898 (Geison 1987).

Martin, career and personal life

But Martin didn't live to see this new journal. His health began to fail soon after his arrival in Baltimore, according to some sources as a consequence of alcoholism. In 1879, he married Hetty Cary, the widow of Confederate General John Pegram. Somewhat older and more socially prominent than her husband, Hetty gave him greater access to Baltimore society, which aided his advocacy for Johns Hopkins. She died in 1892 and just a few months later he resigned from his chair, shortly before the opening of the Medical School in 1893, and he returned to England, dying at the early age of 48 in Burley-in-Wharfedale in Yorkshire. In addition to all his efforts to develop, promote and nurture physiology, he had maintained his own researches. In 1881, for example, he developed the first isolated mammalian heart lung preparation, which Ernest Starling later used to great effect (Breathnach 1969), and in a eulogy in Colorado, Michael Foster is quoted as having said '*So if I have done nothing more, at all events I sent Henry Newell Martin to America*' (Sewall 1911).

References

Appel T (1987). 'Founding' in History of the American Physiological Society: the first century, 1887-1987. American Physiological Society, Bethesda MA, pp.11-29

Breathnach CS (1969). Henry Newell Martin (1848-1893). A pioneer physiologist. *Med Hist* **13,** 271-279

Foster M (1900). *Colorado Med. J.*, cited by Sewall.

Fye WB (1986). H. Newell Martin and the isolated heart preparation: The link between the frog and open heart surgery. *Circulation* **73**, 857-864

Geison G (1987) 'International relations and domestic elites in American physiology, 1900-1940 ' in Geison GL (ed) Physiology in the American context, 1850-1940 American Physiological Society, Bethesda, MA, pp 115-154

Huxley TH, assisted by Martin HN (1875). A course of practical instruction in elementary biology. Macmillan, London.

Maienschein J (1987). Physiology, biology, and the advent of physiological morphology. In: Geison GL (ed). Physiology in the American Context 1850-1940. American Physiological Society, Bethesda, Maryland, pp.177-193

Sewall H (1911). Henry Newell Martin, Professor of Biology in Johns Hopkins University, 1876-1893. *Johns Hopkins Hosp Bull* **22,** 327-33

Sharpey-Schafer E (1927). History of the Physiological Society during its first fifty years, 1876-1926. *J Physiol* **64** (Suppl. 3), 1-76

Reaching out to future physiologists

An insight into the work of The Society's Education and Outreach team

Chrissy Stokes

Head of Education & Outreach,
The Physiological Society

Physiology is more than labs and textbooks, it is a community that benefits from a hub provided by The Physiological Society. Once run by the Members, The Society is now run for the Members by staff working at the Headquarters in London. Under the guidance and expertise of the Council of Trustees, staff ensure that The Society fulfils its Charitable Objects.

Formed in 2011, the Education and Outreach (E&O) Committee is one of six Committees that sit under Council. The Committee meets formally twice per year, when proposals are considered, activities are assessed, issues are discussed and budgets are put together for consideration by Council. Together with Angela Breslin (Education Manager) and Anisha Tailor (Outreach Officer), I am responsible for ensuring the delivery of activities agreed by this Committee.

I was lucky enough to have a great Biology teacher who knew and understood the word 'physiology' and that you could actually study a degree in it. Many people aren't so lucky: physiology is not a word commonly recognised by schools or the public. I see changing this as an opportunity to enhance delivery of The Society's charitable objectives (**www.physoc.org/our-charitable-objects**).

Everyone, at some point in their lives, wonders how their body works – one of our 2015 Public Engagement Grant holders made a whole roadshow out of eating, pooing and sleeping (*PN* 102) – and this is a great hook to engage school students that might become our future membership, your collaborators and maybe one day President of The Society. The E&O team at The Society, guided by the E&O Committee, is here to facilitate and encourage this adventure of exploration.

I have been at The Society since 2007; it really is my ideal job – working with great people (staff and Members) with an important mission and lots of opportunity to learn along the way. And no two days are the same!

Each year, the team manages grant schemes, attends school and public engagement events, develops resources, runs competitions, and feeds into policy work surrounding schools and the curriculum. We also run the activities of: the Education and Teaching Theme and the History & Archives Committee. This list is by no means exhaustive, but I hope you get the picture of the breadth of our work. More information on specific activities can be found on our schools and outreach website – Understanding Life (**www.understanding-life.org/**) – and on The Society's main website.

Although our work is broad, it is carefully considered and assessed by the E&O committee to ensure it continues to fulfil The Society's strategic objectives, and has a positive impact on the progression of physiology and the wider scientific landscape Just this year, the committee is conducting a thorough review of our research grant scheme and techniques workshop funding. Light touch annual reviews/end of grant reviews for other activities will continue as usual. Results of such reviews, new activities and large scale projects are periodically reported to Council in the form of minutes and presentations – this ensures Society activities remain confluent and in line with the overall strategic objectives.

I thought it might be interesting to follow the life cycle of one of our schemes to see how decisions are made and new activities are implemented. I have selected one of The Society's new-er schemes, that has been implemented since I began at The Society to illustrate this life cycle.

In 2011, the E&O Committee realised that reaching new audiences would be possible if science was delivered through non-traditional routes (not in an educational environment). Furthermore, by bringing together physiologists with expert communicators, all parties would benefit (the physiologists would learn from the communicators, the communicators would have access to new funding opportunities, and The Society's funding would be well spent).

The Committee envisaged that these audiences would be distinct from those reached through the pre-existing Outreach Grant scheme, which was specifically designed for Members to deliver a small scale activity, usually within an educational environment – such as a school, university or science fair.

The Committee agreed to commit funding through a new Public Engagement Grant scheme to support activities in 2012. In the first year, under the guidance of the Committee, the team worked closely with providers – such as 'Bright Club'[1] and 'I'm a Scientist Get Me Out of Here!'[2] – to develop strong proposals that would run as example activities. There was also a defined allocation of funding for additional proposals submitted by external providers. From 23 proposals, our first public engagement grant was funded (a project to develop interactive physiology workshops in schools). The high quality and quantity of proposals, coupled with the excellent evaluation reports received, convinced the E&O Committee to continue investing in the scheme. This year, 42 proposals were submitted for 6 available Public Engagements Grants; all the funding was allocated, and you can read more about the proposals on The Society's website: **www.physoc.org/public-events**.

Many of the activities run by the E&O Committee are not delivered in isolation and, in some areas, collaboration with other like-minded organisations and other internal departments is beneficial. An example is the E&O Committee's work on the status and valuation of teachers in Higher Education; this included a collaboration with the Policy Committee, the Academy of Medical Sciences, the Royal Society of Biology and the Heads of University Bioscience departments. A joint report was published, which can be downloaded from our website, and, following the recommendations of this report, the E&O Committee published the booklet '*Recognising Teachers in the Life Sciences*' – a review of which can be found on Page 15.

Of course, none of this would be possible without the support of our Members; the team has met some great people in our quest to deliver all these activities, on time, fit for purpose and on budget.

If you have any feedback on the work of the E&O Committee, please contact me via email **cstokes@physoc.org**.

Meet the other members of our Education and Outreach team:

Anisha Tailor

Outreach Officer

I have a background in Chemistry and, while I may not be an expert in physiology, I have a passion for learning and love finding out about what our Members do. To help me share my fascination for science with others I did a Masters in Science Communication, and then joined the PhySoc family. I have been working here for 3 years, during which time I took a sabbatical in Ghana to set up an education project to support practical based learning in resource constrained environments.

Angela Breslin

Education Manager

With a life science degree and teacher training under my belt, this role offered the perfect opportunity for me to use this experience in order to support teachers and science education. I've been working here for nearly seven years now, and really enjoy the days when I get to visit schools and go to science festivals.

[1] Bright Club is an evening joining together research and comedy. Academics (after some training form the Bright Club team and stand-up comics) take to the stage to share what they do with a friendly informal audience.

[2] 'I'm a Scientist Get me out of here' is an online 'X-factor' style competition between scientists where students are the judges. Over a two week period five scientist are pitted against each other while students bombard them with questions about anything they want. Scientists are voted off one by one, with the students favourite winning £500 to communicate their work to the public.

Ode to Physiology: Animal Olympics!

We are delighted to announce that Charlie Toogood, Vismaya Kharkar and Rose McKerell are the winners of our recent poetry competition 'Ode to Physiology: Animal Olympics!'

We received over 100 entries to the competition which challenged participants to explore physiology through the medium of poetry. With some artistic licence entrants discussed the biological basis of elite performance using rhythm and rhyme. While the poems haven't been checked for accuracy, we are delighted so many people engaged with the competition and expressed an interest in the science of life. A big thank you to everyone who took part!

Our expert judges Kelly Swain, poet in residence at Oxford University Museum, and Sian Hickson, previously an English teacher and now Director of Eureka Edinburgh, whittled down the entries to just one winner from the under 10s, 11-18s and the over 18s categories.

Under 10s

Big and blue – can you guess who?

Charlie Toogood

The cheetah would never have met this creature;
A massive blowhole is its best feature.
This is the nostril of the great beast,
Who usually adores a krill feast.
Every day it eats 8000 pounds,
If I ate that much, I would be round!
The milk tastes like liver and chalk, people say,
But the babies still drink 50 gallons a day!
150 tons is its weight, It's the biggest animal, isn't that great?
With a life span 110 years long,
It's the BLUE WHALE!
Did you guess right or wrong?

11 – 18s

Ode to the Hummingbird

Vismaya Kharkar

Just lighter than a copper pence,
With ropy muscle and wings of gold he floats,
His beak is sharp and needle-thin,
Soft feathers thinner than waves make up his coat.
From flower to flower he hovers and glides
Sucking sweet nectar from each in turn
For whenever he stops, from life he slides
Falling into a torpor
Deep and slow.
His heart flutters, powerful.
Nearly twenty beats a second, but at what cost?
He is founded upon excellence, and without it, he will sleep.
A modern aurora – tiny, gold, and shining
To awaken at the touch of nectar or a new day

Over 18s

Ode to Physiology: Who am I?

Rose McKerrel

To give you a clue to my chosen athlete
Here are some features which make it elite
Its heart is amazing in strength, size and rate
When running flat out –
pulse can increase times eight!
The lungs can expand to fill most of the chest,
Oxygenating blood is what they do best,
When running the guts move forward and back.
Like a piston they help fill those little air sacs...
The limb bones are reduced to run on one toe
And the lack of a collarbone
lets the front leg just flow
The muscles are huge at the top they must go
When the fibres contract –
some are fast , some are slow
The ligaments stretch to take all the strain
Then act like a catapult – forward again
Narrow in front with an elegant head
The air rushes past – for speed they are bred
But what is most clever is it isn't just fast
This animal has stamina- it really can last
It can win at eight furlongs
or stay for the course.
Because as you've guessed –
my favourite's the horse!
Adapted for speed. Adapted to stay.
The horse is my winner every day
And there's one other feature of which science hasn't told
The horse's second heart –
the one made of gold!

Staff structure

The Journal of Physiology

Special issues

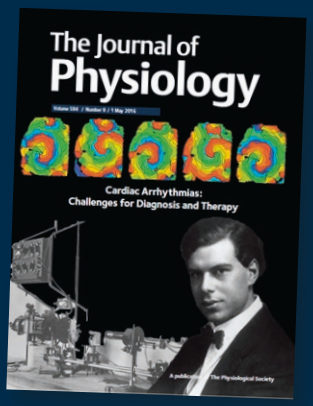
Cardiac Arrhythmias: Challenges for Diagnosis and Treatment

Volume 594, issue 8, May 2016

Despite his early death, George Ralph Mines made transformational contributions to cardiac electrophysiology. This issue is based on a symposium held at McGill University in 2014 to commemorate the centenary of the death of Mines and focused on identifying areas in which basic physiology and theoretical modelling are defining new approaches to clinical cardiac electrophysiology.

Cardiac Autonomic Control in Health and Disease

Volume 594, issue 14, July 2016



This special issue includes three white papers that summarize the current state of understanding for 'Molecular and Cellular Neurocardiology' (Habecker *et al.*, 2016), 'Translational (preclinical) Neurocardiology' (Ardell *et al.*, 2016) and 'Clinical Neurocardiology' (Shivkumar *et al.*, 2016).

These white papers represent the combined efforts of 39 leading international experts in the field and highlight the cellular, organ level and clinical aspects of neurocardiology. They summarize data derived from normal and pathological states. These papers also provide mechanistic insights into several emerging applications of autonomic regulation therapy for cardiovascular diseases.

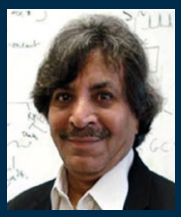
New CrossTalk debate

Does metabolic syndrome cause sleep apnoea or does sleep apnoea cause metabolic syndrome? Explore the augments for both sides in our latest CrossTalk debate by Craig L. Phillips, Camilla M. Hoyos, Brendon J. Yee and Ronald R. Grunstein on one side and Alexandros N. Vgontzas, Jordan Gaines, Silke Ryan and Walter T. McNicholas on the other.

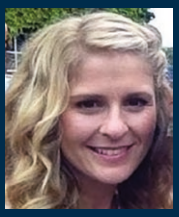
Experimental Physiology

NOW published in EP from Physiology 2016 meeting:

Prize Lectures articles



De Burgh Daly Lecture by Nanduri Prabhakar
Carotid body chemoreflex: A driver of autonomic abnormalities in sleep-apnoea



Society Sharpey-Schafer Prize Lecture by Emma Hart
Human hypertension, sympathetic activity and the selfish brain

Paton Prize Lecture by Bert Sakmann
From single cells & single columns to cortical networks: coincidence detection and synaptic transmission in brain slices and brains

EP symposium

Reports and video introduction to the Symposium on Circadian regulation of cardiovascular and kidney function organised by David Pollock: physoc.onlinelibrary.wiley.com/hub/issue/10.1113/eph.2016.101.issue-8/

Experimental Physiology Prizes

The 2016 Inaugural review prize was awarded to Eoin Cummins of University College Dublin. His review on **Respiratory gases and the regulation of transcription** has been published in the August issue.

The Early career author prize (for articles published in 2015) was awarded to Shingo Takada, Hokkaido University for **Curcumin ameliorates skeletal muscle atrophy in type 1 diabetic mice by inhibiting protein ubiquitination**

Melissa Erickson of the University of Georgia received the runner up award for **Skeletal muscle oxidative capacity in patients with cystic fibrosis**

EP workshops

Editor in Chief Paul Mcloughlin chaired a workshop on 'How to publish your data; meeting the new standards required by regulatory and funding agencies'. This was extremely well attended. If you missed it you can watch it online at http://livestream.com/refinerytv/physiology2016. Paul also met potential contributors with Mike Tipton who will take over as Editor in Chief in October (See the article covering Mike Tipton's research background 'Cold Wet and Nasty' on page 18 of this magazine).

Physiological Reports

A new Associate Editor

As of September 2016, Dr Robert Semple is joining the *Physiological Reports* team of Associate Editors. Robert will take the place of Professor Julian Davis, who is stepping down. Julian has been an Associate Editor since the journal's launch and his clinical expertise has been a key strength of the team.

Robert is an Honorary Consultant Endocrinologist at the University of Cambridge Metabolic Research Laboratories, where he has a research fellowship from the Wellcome Trust. In 2015 he was the winner of the Society for Endocrinology's Starling Medal, which recognises excellence in UK research. His main research interests are centred on the pathophysiology of abnormal insulin action in human disease, particularly disorders in which these metabolic disturbances result in abnormal growth.

PR expands its range

Following the success of Case Studies, *Physiological Reports* has opened its doors to review articles. Like the rest of the journal's content, reviews will be published as Open Access, free to readers and permitting re-use under a Creative Commons CC BY licence. There is a 3,000-word limit.

As with research papers, reviews that are submitted to *JP*, *EP* and the APS journals but don't find a home there will be cascaded to *PR* at the authors' discretion. Reviews can also be submitted direct and the editorial team will be commissioning some in areas they feel will be of particular interest to readers.

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