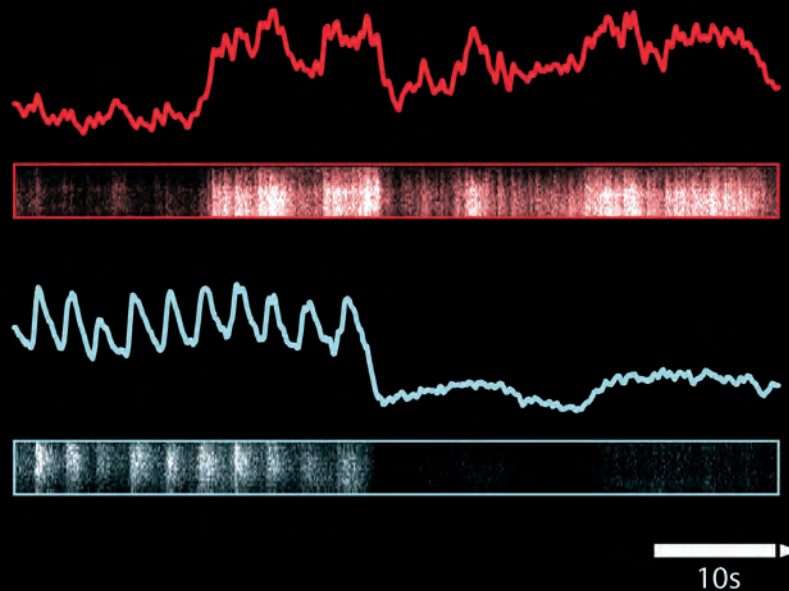
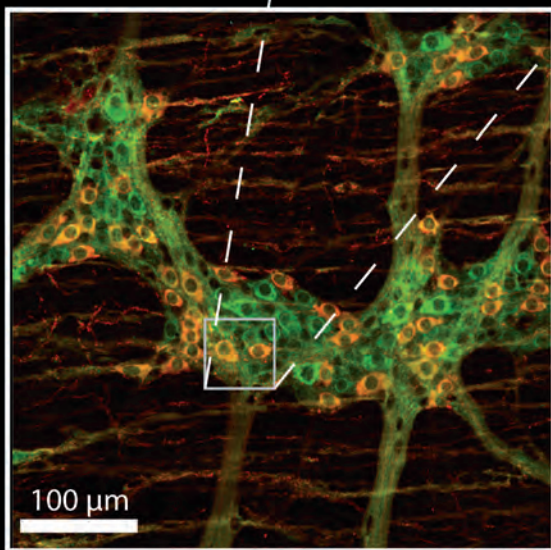
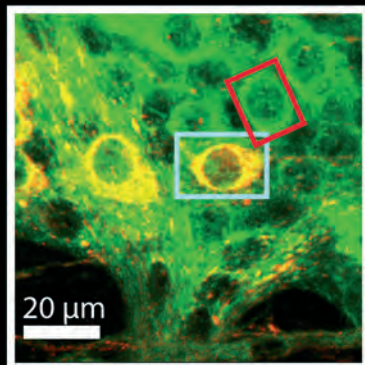


PHYSIOLOGY NEWS

autumn 2010 number 80



Tim Biscoe presents a case for the importance of basic research
HIT to get fit: is it as good as high-volume continuous exercise?
Lymphatic vessels: absorptive sumps or leaky pumps?
The Society techniques workshops

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The Society's dog. 'Rudolf Magnus gave me to Charles Sherrington, who gave me to Henry Dale, who gave me to The Physiological Society in October 1942'

Published quarterly by The Physiological Society

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ISSN 1476-7996 (Print)

ISSN 2041-6512 (Online)

The Physiological Society is registered in England as a company limited by guarantee: No 323575.

Registered office: Peer House, Verulam Street, London WC1X 8LZ.

Registered Charity: No 211585.

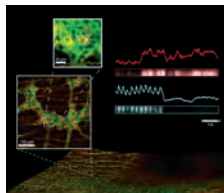
Printed by The Lavenham Press Ltd

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Advancing the science of life



Cover image: Structural and functional analysis of myenteric neurons in the myenteric plexus, from Bayguinov *et al.* p. 29.

PHYSIOLOGY NEWS

Action points

Grants

The Society offers funding through the following grant schemes: Travel Grants, Non-Society Symposia Grants, Outreach Grants, International Teaching and Research Grants and the Vacation Studentship and Departmental Seminar Schemes. For full information, please visit: www.physoc.org/grants

Membership applications

Applications for membership of The Physiological Society are considered on a rolling basis, and a decision is normally made within 15 working days. For full information, please visit: www.physoc.org/membership

Is your membership information correct?

Please check and update your details at www.physoc.org, under 'My Physoc Profile'.

Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Winter 2010 issue, No. 81, should reach the Publications Office (magazine@physoc.org) by **7 October 2010**. Short news items and letters are encouraged, and can usually be included as late copy if space permits.

Suggestions for articles

Suggestions for future articles are welcome. Please contact either the Editorial Administrator or a member of the Editorial Board of *Physiology News* (see contents page for details).

Physiology News online

Physiology News online:
www.physoc.org

Guidelines for contributors

These guidelines are intended to assist authors in writing their contributions and to reduce the subsequent editing process. The Editorial Board of *Physiology News* tries to ensure that all articles are written in a journalistic style so that they will have an immediate interest value for a wide readership and will be readable and comprehensible to non-experts. Scientific articles should give a good overview of a field rather than focus entirely on the authors' own research.

Format of articles

The main message or question posed should be introduced in the first paragraph. The background for the topic should then be established, leading up to the final conclusion.

Length of articles

This will be determined by the subject matter and agreed with the Senior Production Editor.

Submission of articles

Authors should submit articles as a Word document attached to an email. Illustrations should be sent as separate attachments (see below) and not embedded in the text.

Illustrations and authors' photographs

Authors are encouraged to submit diagrams, drawings, photographs or other artwork with their articles and a photograph of the author(s) should accompany submissions. Illustrations and photographs may be colour or black and white, and preferably TIFF, JPEG, PNG, PDF or AI files with a **minimum resolution of 300 dpi**.

References

Authors are requested to keep the number of references to a minimum – preferably no more than two or three. Please cite all references in the style of *The Journal of Physiology* (see *Information and Guidance for Authors* at <http://jp.physoc.org>).

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In this issue

Welcome to the Autumn 2010
Physiology News.

We live in uncertain times for science funding, at least in the UK. The new UK Government is carrying out a 'comprehensive spending review', with cuts to science predicted, and increased drive to selectivity and 'Impact assessments' expected. Liz Bell surveys the new parliamentary landscape for science on p. 42, while on p. 9 Tim Biscoe makes a fascinating case for basic science, finding historical support in all sorts of unexpected places.

Summer is meetings season, and as I write we have recently completed the Society's largest ever Summer Meeting, Physiology 2010, with over a thousand participants. The need for continued focus on Education and Engagement programmes, in order to communicate the many successes of this thriving scientific community to the wider world, comes through strongly from Sense About Science and from the Society of Biology on p. 38–39.

Among our scientific features, the Techniques series continues with the vital but not always so popular topic of statistics, specifically multiple regression (p. 12). And I was fascinated by the article by Joshua Scallan and Virginia Huxley on those least studied of the body's vessels, the lymphatics (p. 16). I have the subjective impression that the vessel interest 'hierarchy' runs arteries > veins > capillaries > lymphatics – but anyone who ever teaches about acute pulmonary oedema knows the importance of lymphatic physiology too.

Finally, on p. 51 we say goodbye to a giant of 20th century physiology and biophysics, Professor Richard Keynes. Chris Huang's wonderful appreciation does full justice to Keynes' breadth of interests and achievements.

Austin Elliott
Editor

Super – or just over the top?

Recently I came across a job advertisement for a 'Super Science Fellow' (sic) at an antipodean university. Trying to suppress the image of a post-doc wearing brightly coloured underpants over a tight white body suit whilst focusing on a specimen with his laser confocal vision – who needs a microscope – I tried to work out exactly what warranted the 'super' in the job title. And for which noun is the adjective intended, I wondered – the science, or the fellow?

It appears that a number of these fellowships have been awarded to universities by the Australian Research Council. As far as I can tell they consist of a three-year contract for early-career post-docs with a better-than-usual track record. The projects to which these super science fellows would be assigned involved a number of '-omics'. Nothing very unusual there. So what's wrong with 'Post-doctoral Research Fellow'? Does it project the wrong image? Not progressive enough? Not 'super'?

There is an obsession in science (and in academia generally) with inventing new catchphrases, degrees, job titles and names for departments. Clearly, as science is about discovery, there is sometimes a legitimate need to invent new words. However, why this should extend to the replacement of perfectly adequate ones, such as 'research fellow', by others that have more than a hint of the ludicrous, is puzzling. Part of the problem is perhaps that science must be seen to beget *innovation* – widely regarded, by politicians at least, as a key driver of economic growth. This is coupled with a belief in political quarters that innovation can somehow be managed. The scientific process is painstakingly time-consuming, with relatively low productivity for the amount of time invested – though not so much, I would argue, for the amount of money. This need for time is at odds with immediacy of the

modern world, in which technology, originally spawned from scientific discovery, provides information instantly at the click of a mouse. Note that, less than half a century ago, the previous sentence would have been unintelligible, or at best the stuff of science fiction.

Physiology, with its systems approach to experimentation and its heavy dependence on *in vivo* work, may be perceived as stuck in a time warp by these modern standards. Even though the word 'physiology' itself is still widely used in many contexts (see Editorial, PN75), in recent years we have seen our departments and degrees gradually disguised as something else – 'biomedical sciences', for instance. We are not the only victims of such word erosion; analytical chemistry degrees have morphed into forensic science, spurred by the popularity of television dramas such as *Silent Witness* and *Waking the Dead*. And of course there is hardly a university that does not declare somewhere on its web site – probably multiple times – that its research is 'world-class'.

This is a bit of a slippery slope. As things new become commonplace, and snappy modern words lose their cutting edge with wear, we move on to the *next* big thing or buzzword – all to feed the illusion of rapid progress. It would seem that nowadays the PR is almost (at least?) as important as the research itself.

Science certainly keeps progressing, but perhaps not quite to the extent, or at the speed, that the PR spiel

would have us believe. Indeed, it is now getting increasingly common to see scientists criticised for *overstating* the case for science, or at least for science funding.

Perhaps, then, we need to make a more concerted effort not to let the language get too far ahead of the reality.

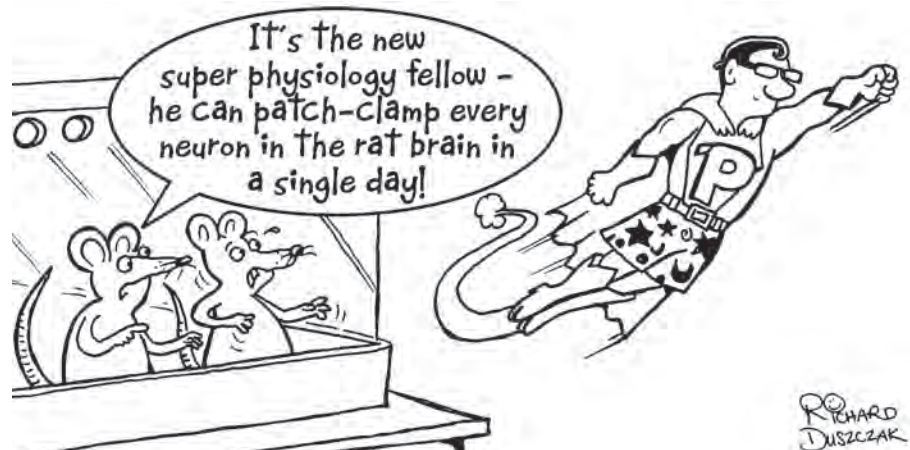
Patricia de Winter

Reader Survey

We have now completed our *Physiology News* reader survey. The results were very pleasing, showing that all sections of the magazine were read. Feature articles, Society News, the *Unbelievable!* satire column and – surprisingly? – Editorials proved especially popular. The overall mix of content was judged '*about right*' by almost all respondents. Many indicated they kept copies or passed them on to colleagues and lab members, with only a third of copies ending up in the paper recycling bin. Most respondents judged PN '*as good as or better than*' other society magazines they read, and felt it did a good job of encouraging people to become Members of The Society.

Our thanks to all The Society Members (and non-members) who took the time to reply.

Congratulations to Julien Brugniaux from University of Glamorgan, who won the prize for completing the questionnaire. He wins an Acer Aspire One netbook.



Physiology 2010, University of Manchester

30 June–1 July

“For Manchester is the place where people do things... ‘Don’t talk about what you are going to do, do it.’ That is the Manchester habit. And in the past through the manifestation of this quality the word Manchester became a synonym for energy and freedom and the right to do and to think without shackles.” From “What the Judge Saw” by Judge Parry, 1912.

Physiology 2010 fast facts

1009 registered participants
597 Members of The Society
25 Exhibitors
11 Sponsors
6 Themes
5 Prize Lectures
19 Symposia
118 Invited speakers
144 Oral communications
294 Poster communications
1 Annual General Meeting of The Physiological Society
1 Outreach workshop
1 Teaching workshop
1 Commercial workshop
7 Lecture Theatres
800 m² of poster and trade exhibition space
398 at the Welcome Reception at The Manchester Art Gallery
333 at The Society Dinner at Old Trafford, home of Manchester United FC



Quotes from participants:

‘The venue was just the right size, so easy to attend all sessions of interest. The layout encouraged interaction at the posters.’

‘Good meeting – thanks - plenty of time and space to meet people and chat as well as attend the science.’

‘Excellent meeting, well organised, plenty of staff on hand to help out and direct.’

‘Many thanks for a well-organised and enjoyable event. I was sorry I was unable to attend Friday because the programme looked as good as the other two days.’

‘This is the first Physiological Society meeting I have attended and I thoroughly enjoyed it.’

‘This was my first ever conference and all I can say is that I had such a wonderful experience and met so many excellent scientists in my field and enjoyed the meeting a lot.’

‘Enjoyed all of it, from oral communications to socials, a must for Physiology graduates.’

‘Attending such a prestigious Meeting is a professionally rewarding experience for every researcher. For me this meeting represented a opportunity to:

- (i) Listen to state-of-art lectures of world-renowned scientists.*
- (ii) Meet new friends and start to build relationships with other researchers;*
- (iii) Last but not least, improve my understanding of spoken English.’*

‘Really well organised meeting, fun social events, good science and speakers.’

‘Timekeeping in symposia and oral communications was generally excellent. This was very useful to people who, like me, have interests that cross over theme boundaries – thanks!’

‘I spent a very enjoyable day, and appreciated that Society Members seemed to recognise that I was a relatively inexperienced student. Their questions were addressed at an appropriate level for me, and I would





Runner-up: Margaux Horn, University of Manchester, UK

Cellular & Integrative Neuroscience

Winner: **Martin Haustein**, University of Leicester, UK

Runner-up: **Laura Corns**, University of Leeds, UK

Epithelia & Membrane Transport

Winner: **Chong Da Tan**, St George's, University of London, UK

Runner-up: **Louise Evans**, University of Edinburgh, UK

Human & Exercise Physiology

Winner: **Angus Wann**, Queen Mary, University of London, UK

Runner-up: **Wouter Eilers**, Manchester Metropolitan University, UK

Metabolism & Endocrinology

Winner: **Liza Noordin**, University of Strathclyde, UK

Runner-up: **Angela Carvalho**, University of Nottingham, UK

Vascular & Smooth Muscle Physiology

Winner: **Peter Rae**, University of Birmingham, UK

Runner-up: **Fiona Lynch**, University of Manchester, UK

be happy to attend future meetings where possible. Thank you.'

'The provision of lunch at this meeting was excellent and kept people at the conference venue, around the posters and trade stands rather than going elsewhere. Facilities were excellent and all information supplied by Phys Soc was helpful and covered everything you needed.'



Winners of Pfizer Prize

Sam Lane, University of Bristol, UK

Sarah Arrowsmith, University of Liverpool, UK

Ellen Forty, University of Manchester, UK

Phil Robinson, University of Manchester, UK

Rebecca Burton, University of Oxford, UK

Ana M Alviar Baquero, University of Bristol, UK

Winners of The Physiological Society Poster Competition

Cardiac & Respiratory Physiology

Winner: **Aziza El Harchi**, University of Bristol, UK



Mechanosensitivity: from transduction to sensation

Cross Themed Meeting,
Durham University UK, 15 -17
December 2010



All cells need to be able to respond to mechanical stimulation in order to maintain their own integrity. In multicellular animals the ability of cells to exhibit mechanosensitivity is exploited in many different ways, such as the deposition of bone in response to local stresses, the detection and signalling of movement and vibrations in fluids in the ear by highly specialised receptor cells, and the detection of stretch and tension necessary for control of smooth muscle in blood vessels or hollow organs, of posture and of movement, in some cases by the effector cells themselves and in others by complex sense organs. Mechanosensitivity is therefore one of the most fundamentally important of cellular properties, but also one whose molecular basis is least understood. It is therefore, perhaps, especially suitable as the subject of the focused symposium at the Cross Themed Meeting of The



The organisers: Guy Bewick (University of Aberdeen) on the left and Bob Banks (Durham University) on the right.

Society; certainly we have tried to include individual topics to appeal to members of most of The Society's themes.

The meeting will run for two and a half days and will typically be arranged in sessions of one or two invited speakers followed by two shorter oral communications on related topics drawn from the submitted abstracts, the remainder of which will be presented as posters. The first (half) day will be concerned with molecular aspects of mechanotransduction; on the second day the topics will move to the cellular level and will include vascular smooth muscle, osteoblasts and other non-neural systems; and the final day will be concerned with the nervous system – in particular dorsal-root ganglion cells and their peripheral terminals, hair cells, and invertebrate mechanoreceptors – and will end with a round-table discussion. This will be an opportunity to draw together the topics covered across the whole meeting, to emphasize their inter-relatedness and it will provide an ideal forum for cross-fertilization of ideas between them.

The venue for the meeting will be the modern setting of the science laboratories of Durham University. They are just a few minutes' walk from the spectacular cathedral and castle that dominate the peninsula in a loop of the River Wear and that together constitute the heart of a UNESCO World Heritage Site. The castle itself, formerly one of the palaces of the Prince Bishops of Durham, is now a college of the University. The Cathedral, originally

a Benedictine monastery, retains its claustral buildings. Try to take a few moments to walk along the cobbled medieval streets, across one of the ancient bridges to view the river. Or shelter from the December weather in the many cafes, pubs and restaurants. A little to the north of the county boundary, in Northumberland, lies another World Heritage Site – Hadrian's Wall, with numerous other Roman sites nearer to hand, including at Wallsend, Corbridge and South Shields.

Guy Bewick and Bob Banks

Invited Symposium Speakers

- Stephan Kellenberger**
University of Lausanne, Switzerland
- David Beech**
University of Leeds, UK
- Eric Honoré**
IPMC, Valbonne, France
- Thomas Burkholder**
Georgia Institute of Technology, USA
- Heather Drummond**
University of Mississippi Medical Center, USA
- Thomas Gudermann**
University of Munich, Germany
- Tim Skerry**
University of Sheffield, UK
- Renate Pilz**
University of California, San Diego, USA
- Astrid Bakker**
VU University Medical Center, The Netherlands
- Miriam Goodman**
Stanford University, USA
- Gary Lewin**
Max-Delbrück-Centrum, Berlin, Germany
- Laurent Misery**
University Hospital, Brest, France
- Tony Ricci**
Harvard University, USA
- Jonathan Ashmore**
University College London, UK
- Lorraine Pawson**
Syracuse University, USA
- Guy Bewick**
University of Aberdeen, UK
- Andrew French**
Dalhousie University, Canada

Three months in the life of Professor Ole Petersen, Director of the Cardiff School of Biosciences

Ole Petersen became the new Director of Cardiff School of Biosciences earlier this year. Here he answers some questions regarding his move from Liverpool and his plans for the future.

Sarah Hall (SH): What attracted you to the post of Director of the Cardiff School of Biosciences?

Ole Petersen (OP): The Cardiff School of Biosciences is one of the largest and most comprehensive schools of biological sciences in the UK. It has outstanding staff in the fields of biodiversity/ecology, molecular biosciences, pathophysiology and neuroscience. It is an exciting job to lead this school and – in particular – to help the School fully realize its enormous potential in both research and teaching.

SH: Have your first three months in post been as expected?

OP: These first months have been even busier than expected! The Cardiff School of Biosciences is so large and covers such a broad range of topics that it is a major task to get to know all the key individuals and to obtain even a superficial understanding of all the work that is going on. At the same time I have had to continue many heavy international commitments, for example, chairing the European Research Council's Starting Grant Panel for Physiology, Pathophysiology and Endocrinology and chairing *Physiological Reviews'* European Editorial Committee. Of course, I also have to continue my own research work as a Medical Research Council Professor.

SH: Like many universities, Cardiff's Physiology department has been absorbed into a much larger school of Biosciences. How do you anticipate the role of the discipline evolving in the next decade?

OP: Physiology increasingly becomes pathophysiology. Almost all the grant proposals coming to the European Research Council's Starting Grant Panel for Physiology, Pathophysiology and Endocrinology deal with pathophysiological investigations. It is important to understand that these are grant proposals from Europe's leading young scientists to a funding organization that – in contrast to many other funding bodies – selects exclusively on the basis of scientific excellence. The move into pathophysiology is therefore not due



Ole with his wife, Nina Burdakova (Research Support Officer in the Cardiff School of Biosciences), receives his CBE at Buckingham Palace 2008.

to tactical considerations concerning funding opportunities, but rather due to the enormous opportunities that have opened up to attack pathophysiological mechanisms and thereby the fundamental processes by which major diseases are initiated. Pathophysiology is very broad, perhaps even broader than basic physiology, and we physiologists can benefit a great deal from integrating our expertise, for example, in electrophysiology and cell imaging with expertise in molecular and genetic disciplines.

SH: Cardiff and Liverpool are both resurgent cities with a rich maritime history and strong sporting tradition. What similarities and differences have you observed between their universities?

OP: At a superficial level the two universities look rather similar. They are both Russell Group Universities of roughly the same size, with very similar financial turnovers and with very similar overall positions in the league tables and the last RAE. Physiology was traditionally very strong in Liverpool with such towering figures as Sherrington and Gregory, who was

my immediate predecessor as George Holt Professor in Liverpool. During my 17 years as Head of the Department of Physiology in Liverpool, the department was consistently top-rated in all RAEs, the only physiology department in the whole of the UK with such a record. When I stepped down as Head of Department in Liverpool to concentrate on my research activities, the University took the opportunity to integrate physiology into a School of Biomedical Sciences. This did not work so well in the last RAE (2008). I had always resisted this move, not because there is anything wrong in principle with such integration, but simply because it did not make tactical sense to mix up an elite unit with units of lesser research strength. Cardiff integrated the life sciences into a School of Biosciences a number of years ago and has undoubtedly benefited from this integration. Research strength has been more broadly based although the School is of course particularly well known for its mammalian genetics research, signposted by the 2007 Nobel Prize in Physiology or Medicine to Sir Martin Evans, my predecessor as Director of the Cardiff School of Biosciences. I think these examples illustrate that organizational decisions concerning research should be made taking into account the local situation rather than general principles.

SH: What impact do you expect the General Election to have on physiology in particular and academia in general?

(Note: this question was posed just prior to the election on May 6th)

OP: My expectations are pretty low. Science and education have not featured much in the election campaign and there have already been significant cuts in university budgets. It should be blindingly obvious to all that without a very strong science and technology base, the future prosperity of the UK is in grave danger. Just now, it seems that this is much better understood in Germany than in the UK. I had the great privilege of being present at The Royal Society a couple of weeks ago, when Angela Merkel received the Society's King Charles II Medal. Angela Merkel's acceptance speech contained the most strongly expressed support



The School of Biosciences, currently undergoing a facelift/extension (courtesy of the architects Rio architects, Ltd).

for increased financial support for science and education that I have ever heard from a senior politician in power. She has, of course, not only talked about increasing science support, but has actually – even in this time of grave financial problems – markedly increased science funding in Germany, because – as she explained – this is the basis of Germany's future prosperity. Interestingly, she also expressed strong support specifically for the European Research Council and for its insistence on only judging research proposals on the basis of scientific excellence. I asked her whether she would wish that a higher proportion of the EU's research funds should be allocated to the ERC. Her answer was positive. We can only hope that we will at some point in the future again have politicians of this calibre in power in the UK. Meanwhile, we must be happy that the ERC has increasing resources in the coming years and use our still excellent science base – which benefited very much from the strong support of Tony Blair and Lord Sainsbury, when they were in power – to compete effectively in the international market. However, without increasing support from the UK government our current relatively strong position is not sustainable.

SH: What has been your biggest challenge since coming to the Cardiff School of Biosciences?

OP: The biggest challenge facing the School – and this is basically the main challenge also for all other research organizations in the UK – is to continue to explore, at the highest possible intensity, all the wonderful opportunities for exciting new biological research at a time of declining national resources. The School must explore all new funding opportunities – also internationally – and rebalance internally so that every member of staff makes a full

contribution to research and/or teaching.

SH: Have there been any pleasant surprises?

OP: I already knew many outstanding scientists working in the School, but I have now met many more, as well as many superb teachers. I have also seen how valuable it is to have a really good administrative staff, like the one we have in the Cardiff School of Biosciences.

SH: Now that you have settled in, what are your plans for the School and how will you achieve this?

OP: I have already initiated a re-structuring of the School's research into four Divisions: Organisms & Environment, led by Professor Mike Bruford; Molecular Biosciences, led by Professor Jim Murray; Pathophysiology & Repair, led by Professor Alan Clarke and Neuroscience, led by Professor Kevin Fox. Each of these divisions is internationally competitive at the highest level. I have also appointed an International Scientific Advisory Board, including several world-leading physiologists: Kim Barrett from San Diego, Arthur Konnerth from Munich, Michel Lazdunski from Nice and Oleg Krishtal from Kiev. The arrival of my MRC-supported research group in Cardiff has significantly increased the number of physiologists in the School of Biosciences and in collaboration with Professor Paul Kemp and Dr Daniela Riccardi we are now integrating into what I expect will become a very powerful Cell Physiology/Pathophysiology Group working in the crucially important areas of cell signalling. This group will be an important element of the Division of Pathophysiology and Repair and will benefit enormously from the surrounding molecular and genetic expertise.

Society Noticeboard

Scientific Meetings – 2010

For a comprehensive overview visit the website

Cardiac & Respiratory Physiology Themed Meeting

University of Birmingham, 1–3 September

Cross Themed Meeting

Durham University, 15–17 December
Abstract submission and registration open on 11 October

Abstract submission closes 8 November
Early bird deadline 22 November

International Workshop

Mitochondria and oxidative stress in cell signalling

Hacettepe University, Ankara, Turkey, 15–17 September

Joint International workshop of The Physiological Society, the British Pharmacological Society and the Turkish Pharmacological and Physiological Societies

The Journal of Physiology Symposia

Reactive oxygen and nitrogen species in skeletal muscle: acute and long-term effects

Satellite Symposium at XXXIX European Muscle Conference (EMC 2010), Padua, Italy, 11 September

TRP channels: from structure to disease

Festschrift in honour of Bernd Nilius, Leuven, 23–25 September

Microcircuit-specific processing in the hippocampus

Satellite Symposium at SfN 2010, San Diego, CA, USA, Friday, November 12

Society-sponsored meetings

The parental brain: neurobiology, behaviour and the next generation

Informatics Forum, University of Edinburgh, 1–4 September

Transporters, channels and barrier function

Epithelial Biology Meeting, Discovery Point, Dundee, UK, 2–3 September

Ion channels and signalling in the microcirculation

Symposium, Maison de la Chimie, Paris, France, 25–28 September, 9th World Congress for Microcirculation

Irish epithelial physiology meeting

Rivercourt Hotel, Kilkenny, ROI, 21–22 October

Travel Grants

www.physoc.org/grants
www.physoc.org/international

A case for basic research

The Editorial by Patricia de Winter in *Physiology News* 77 about 'Targeted spending' brings to the fore once more the potential for attack on research by our political masters. Though the new British minister for Science and the Universities, David Willetts, has made gratifyingly clear statements about the value and key role of basic research, history shows that it is perilous to leave such things to the politicians.

I thought that re-iteration of some of the arguments and ideas about research in universities would be timely. I should say first that for many years the major defender of UK science research was Save British Science (now CaSE), started by Joe Lamb and Denis Noble of this Society, whilst the details of the case for research were brilliantly documented by John Mulvey of the Department of Physics in Oxford. We owe all of them a debt for those resources, which I have drawn on in writing this.

Not a new problem

A thorough discussion of the problem was given more than 30 years ago by JH Comroe and RD Dripps in their *The Top Ten Clinical Advances in Cardiovascular-Pulmonary Medicine and Surgery* [1]. Another important source is JH Comroe, 1977 [2]. Comroe and Dripps were responding to a US Defence Department Report, *Project Hindsight*, published in 1966–69. They wrote:

"The nation's medical research policy should be based on more than an analysis of weapons development by the Department of Defence and on informal 'let me give you an example' anecdotal arguments by concerned scientists", though examples are necessary.

Comroe and Dripps defined research as *basic* "when the investigator, in addition to observing and measuring, attempts to determine the *mechanisms* responsible for



Tim Biscoe (photo by Martin Rosenburg).

the observed effects". They discuss clinical orientation; where the research was done and by whom; the role of contract-supported or committee-directed research; lags between initial discovery and application; and more. Their methodology was to ask 90 physicians and surgeons to select the top ten clinical advances. They screened more than 6000 articles relating to those advances, picked more than 3400 for tabulation in the report, and of these selected 663 key articles with the help of consultants. Of the 663 articles, 41.6% sought knowledge for the sake of knowledge unrelated to a subsequent clinical advance, and 61.5% described basic research dealing with mechanisms rather than products. Of the key research, 67.4% was done in colleges and universities.

The role of universities and of curiosity

First, *a university is a place where knowledge is being advanced through research and scholarship; where it is understood that knowledge is not complete; and where basic research is done and so the limits of knowledge are explored*. I doubt there is any better statement of the reasons we do research than given by GH Hardy in *A Mathematicians Apology* [3]:

"The first [reason] (without which the rest must come to nothing) is intellectual curiosity, desire to know the truth...

Then, professional pride, anxiety to be satisfied with one's

performance... Finally, ambition, desire for reputation..."

Hardy continues:

"It may be fine to feel, when you have done your work, that you have added to the happiness or alleviated the sufferings of others, but that will not be why you did it. So, if a mathematician, or a chemist, or even a physiologist, were to tell me that the driving force in his work had been the desire to benefit humanity, then I should not believe him (nor should I think the better of him if I did). His dominant motives have been those which I have stated, and in which, surely, there is nothing of which any decent man need be ashamed."

Curiosity and desire to know the truth about a subject are, as Hardy says, the most important reasons to do research. These reasons recur through history.

Socrates: And the third [subject our young men must study] should be astronomy. Or don't you agree?

Glaucon: Yes, I certainly agree. A degree of perception in telling the seasons, months and years is useful not only to the farmer and sailor but equally to the soldier.

Socrates: You amuse me, with your obvious fear that the public will disapprove if the subjects you prescribe don't seem useful. (From Plato's *Republic* VII, 527 [4].)

This understanding is trans-cultural. A succinct comment upon scholarship is found in the *Ta Hsueh* (The Great Learning) [5], translated as "the attainment of knowledge lies in the investigation of things". And elsewhere [6]: "extension of knowledge lay in the investigation of things" and: "things being investigated, knowledge became complete". It is probably anachronistic to say these expressions encompass the sciences, but they nevertheless apply to learning.

Shakespeare understood this too; here is the Duke of Burgundy

speaking about post-war (Agincourt) France in *Henry V*, Act V, scene 2:

“Even so our houses and ourselves
and children
Have lost, or do not learn from want
of time
The sciences that should become our
country
But grow like savages.”

Shakespeare is here clearly not using the word ‘sciences’ in a narrow sense.

In summary, the demand that research should be ‘relevant’, and should meet the needs of Society, is historically opposed. Such demands are easy to make, but the proponents tend not to specify what is relevant nor what are the needs. Rather, they seek top-down direction without knowing the direction! In direct contrast, when research is curiosity-driven, then the pursuit of a conclusion is internally driven by the investigator, not imposed from outside; the enthusiasm of the brightest is thus given free reign.

The demand for relevance has often left the impression that much (or even most) of university research is useless. The resulting censure is levelled just as much against the humanities as against the sciences. This view of university research is false and arises from a serious misunderstanding of purposes; it erroneously equates pure research with ‘useless’ and applied research with ‘useful’.

Green grass and blue skies

A concrete example may serve here. Charles Wilson, Secretary of Defence to President Eisenhower in 1953–57 and a noted opponent of pure research, famously said “I don’t care what makes the grass green”. Comroe pointed out that Wilson might as well have said “I don’t care why the sky is blue”.

The first systematic investigation of the actual question “Why is the sky blue?” was carried out by the physicist John Tyndall, friend of and successor to Michael Faraday at the Royal Institution (see [2]). Tyndall:

1. Showed why the sky is blue, namely because of the presence of small particles in the atmosphere that scatter light.
2. Gave the final blow to the theory of spontaneous generation using his development of a method to establish the elimination of small particles from gases.
3. Demonstrated the respiratory system is defended by a system that filtered out particles.
4. Gave the first observations of the anti-bacterial actions of *Penicillium* whilst investigating particles in air during studies on measuring turbidity.
5. Demonstrated conduction of light in a curved stream of water, and so provided the theoretical basis for the flexible bronchoscope and other endoscopes.

Not bad for investigating the blueness of sky.

So how can it be known what will be relevant in ten years time, except in a very general sense? The argument confuses categories of knowledge. There is basic research, which leads to the creation of a body of knowledge. Out of that body of knowledge may spring technology. It is the technology that may be seen as relevant to the needs of the society. Technical education is of outstanding importance, and has been catastrophically neglected in Britain. But it is not necessarily best carried forward by university people, and is, one might think, best done in a technical environment.

So Research Universities must sustain an environment that will best allow development of critical competence, of skills at assessing evidence, and of making judgements. There should be an environment that will promote the questioning of authoritarian unreasoned views, yours and mine – an environment in which young people learn to doubt, to express themselves, and to articulate their ideas and explore them with enthusiasm. Thus can be promoted the generation and transmission of new ideas, and of the

fact that knowledge is not complete; and that is what is relevant to the future of our society. New ideas will not germinate if we focus only on what is deemed to be relevant at the moment, or on what is known at present. A focus on producing a more efficient steam engine will never lead to the development of electricity as a source of power; rather, it will lead to the more efficient utilisation of steam. That may be important, but it will not be revolutionary.

A little thought will bring many examples of key basic research to mind. For physiologists many may have a medical context. Some examples of what I think of as basic discoveries which led eventually to practical advantages are given in the box, but clearly this list is very far from complete, and most readers will be easily able to compile their own equally partial list. Where, for example, does one place the whole of molecular biology since 1953? The list will, I hope, be a stimulus to others to make their own.

Doubts and questions

We must, above all, preserve the most important academic freedom – the freedom to doubt and to question received views. From the freedom and willingness to recognise our ignorance, and from the freedom to pursue the consequences of that recognition, springs unexpected insight into the human condition and the nature of the universe.

It is always worthwhile to read Richard Feynman. In this context, in his 1955 lecture *The Value of Science* [8], he argues that we must develop a satisfactory philosophy of ignorance – for with it come the fruits of freedom of thought. The freedom of intellectual exchange predicates international exchange with any other university or the great academies. We should, by example, illustrate the merits of absolute integrity, rigour and openness in discourse. Without these things education is of little value, our research will fail to prosper, and our scholarship will die.

So what to do? We all can, and we should, write to our elected representatives – our MPs. They attend to their post bag. Some will argue that attempts to intervene in the body politic are a waste of

time. That may turn out to be so, but we know for certain that if we do not attempt to intervene we will have no influence at all. Some might argue that The Physiological Society is a Charity, and cannot therefore

enter the lists. That is not so. We are clearly allowed in law to argue, in public, our case for our charitable purposes. In the 1980s we did this in respect to animal experiment legislation, including in the Palace of Westminster. We should argue for physiology, and for science, at every opportunity, if we think our cause is just. It is my hope that The Society, along with the other biological societies, will take the lead in this. For, if you will forgive me another literary reference to close with, “We have miles to go before we sleep” [9].

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 2. Comroe JH (1977). *Retrospectroscope, Insights into Medical Discovery*, Von Gehr Press, CA; this is a compilation of a series of articles that first appeared in the American Review of Respiratory Disease, 1975–77
 3. Hardy GH. *A Mathematician's Apology* was first published in 1940. In the 1967 edition, published by CUP with a foreword by CP Snow, the quotation is found on p. 79, in Hardy's chap. 7.
 4. Plato. *The Republic VII*, p. 527. In the 1987 Penguin edition the passage quoted is found on p. 335 at the beginning of a section 'III. Solid Geometry'. The remainder of this passage is concerned in part with the issue of learning useful things.
 5. *Science and Civilisation in China* by Joseph Needham, vol. I, p. 48. CUP (1954).
 6. *The Chinese Classics* by James Legge, vol. I, p. 358. Hong Kong University Press, 1960.
 7. *Macbeth*, Act I, Scene 3, Lines 58–60.
 8. Richard Feynman in *What do you care what other people think*, pp.230–248. Unwin Paperbacks 1990.
 9. Robert Frost, 'Stopping by woods on a snowy evening':
“The woods are lovely, dark and deep,
But I have promises to keep,
And miles to go before I sleep,
And miles to go before I sleep”.
- from “New Hampshire” (1923). See, for example, in *Selected Poems* published by Penguin, 1973.

Examples of key research

1. Harvey, 1628, de motu cordis
2. Wren, 1665, I.V. injection
3. Hooke, 1665, with microscope described cells in plants
4. Hooke, 1667, venous blood → red in air
5. Hales, 1733, haemastatics, first recording of arterial pressure and other variables
6. Franklin, 1752, flies kite in thunderstorm. Collects electrical charge
7. Priestly, 1775, discovery of oxygen
8. Galvani, 1780, animal electricity
9. Jenner, 1798, vaccination
10. Volta, 1800, electricity generated by dissimilar metals; battery
11. Faraday, 1818, action of ether on a gentleman
12. Poiseuille, 1840, flow of liquids in tubes
13. Du Bois Reymond, 1843, electric current in nerve activity as well as in muscle
14. Weber & Weber, 1846, vagus stimulation stops the heart
15. Bernard, 1878, *milieu interieur*
16. Arrhenius, 1883, ionisation and the hydrogen ion
17. Ringer, 1883, Ca and K necessary for *in vitro* tissues
18. Oliver & Sharpey, 1895, adrenal extract raises blood pressure
19. Becquerel, 1896, radioactivity in uranium
20. Landsteiner, 1900, blood groups
21. Bayliss & Starling, 1904, first hormone, secretin
22. Langley, 1905, course of the sympathetic nerves and site of ganglia
23. Hopkins, 1913, importance of enzymes
24. Dale, 1914, actions of acetylcholine
25. Banting, Best, Collip & McLeod 1922, discovery, purification and administration of insulin
26. Gasser & Erlanger, 1922, oscilloscope for recording rapid events
27. Avery & Dubos, 1930, soil as a source of anti-bacterials; Schatz & Waksman, 1944, streptomycin isolated
28. Ruska, 1934, high resolution e.m.
29. Young, 1936, described Squid giant axon
30. Florey *et al.* 1940 *et seq*, isolation and development of penicillin
31. Norman Borlaug, 1944 *et seq*, revolutionary wheat yields harvested in Mexico, India and Pakistan from new cereal strains
32. Bardeen, Brattain & Shockley, 1948, transistor
33. Hodgkin & Katz, 1948, changes in Na and K permeability in Squid axon
34. Enders, Weller & Robins, 1949, cultivation of poliomyelitis virus *in vitro*
35. Lewis, 1950s *et seq*, homeotic genes and development
36. Fatt & Katz, 1951, miniature end plate potentials
37. Brock, Coombs & Eccles, 1952, inhibitory post-synaptic potential
38. Hodgkin & Huxley, 1952, transmembrane action potential recording
39. Watson & Crick, 1953, double helix for DNA. Subsequent development of understanding of the genetic code and how proteins are made
40. Brown & Goldstein, 1976, low density lipoprotein receptors
41. Etc.

It is a simple matter to track these discoveries on the internet.

Multiple regression

In this Techniques article Peter Cahusac explains multiple regression, a much used statistical procedure, but one that is frequently misunderstood or misused. Multiple regression allows the effects of many explanatory (independent) variables on the measured (dependent) variable to be analysed simultaneously for situations when a single explanatory variable fails to account for most of the variation in the dependent variable – a common occurrence. If you have ideas for future Techniques articles please email magazine@physoc.org.

We all know that correlation is a useful statistical technique widely used to assess the linear relationship between two variables. The correlation coefficient tells us the extent to which points in a scatter plot conform to a straight line, and by its polarity whether the relationship is positive or negative. The closely related technique of regression quantifies the relationship between the variables by providing an equation for the linear relationship in terms of slope and intercept, and therefore allows the prediction of values. Multiple regression takes the analysis one step further by allowing more than one independent variable (IV) to be used to predict (or explain) the dependent variable (DV). Using multiple predictors reflects more accurately the true relationship between variables – few phenomena

are dependent on a single IV. Multiple regression is a flexible statistical technique with wide general applicability. However, perhaps because of this flexibility, it is open to misuse and abuse. Tabachnick & Fidell (2007) is an excellent reference for multiple regression and other multivariate methods.

I have made up a small data set to illustrate how the technique can be useful (see Table 1). Let us say I recruited some athletes, mainly elite sporty types (Elite), but to make up numbers, a few others whose only interest in sport is watching it on TV (couch potatoes). I am interested in heart rate changes (DV) in response to the type of activity and intensity of exercise (IVs). Each participant was randomly selected to carry out a specified type of activity (walk, jog, sprint), while intensity was measured by the exercise machine on a scale from 0 to 20. Heart rate was



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measured at the end of the specified activity.

A scatter plot of the data, heart rate against exercise intensity, is shown in Fig. 1. The types of activity are indicated by different symbols in the plot. The line is the regression line (line of 'best fit') for heart rate on exercise intensity. Simple correlations between all four variables are shown in Table 2.

The simple correlation between heart rate and exercise intensity

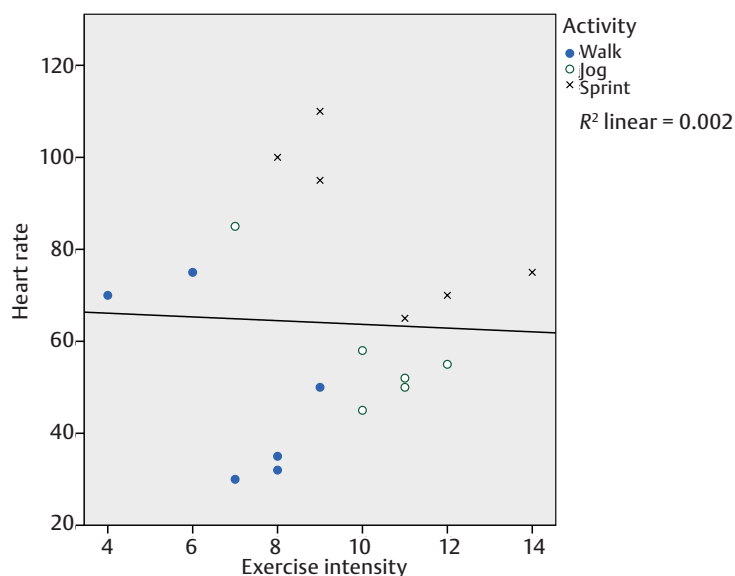


Figure 1. Scatter plot.

Table 1.

Heart rate	Intensity	Activity	Athlete
30	7	walk	Elite
35	8	walk	Elite
50	9	walk	Elite
32	8	walk	Elite
45	10	jog	Elite
50	11	jog	Elite
55	12	jog	Elite
52	11	jog	Elite
58	10	jog	Elite
65	11	sprint	Elite
70	12	sprint	Elite
75	14	sprint	Elite
70	4	walk	Couch potato
75	6	walk	Couch potato
85	7	jog	Couch potato
110	9	sprint	Couch potato
95	9	sprint	Couch potato
100	8	sprint	Couch potato

Table 2. Simple correlation coefficients for the data in Table 1. For all analyses, type of activity is coded as: 1, walk; 2, jog; 3, sprint; and type of athlete is coded as: 0, elite; 1, couch potato

Correlations				
		Exercise intensity	Activity	Type of athlete
Heart rate	Pearson Correlation	-.043	.672	.789
	p value (2-tailed)	.867	.002	.000
Exercise intensity	Pearson Correlation		.603	-.613
	p value (2-tailed)		.008	.007
Activity	Pearson Correlation			.144
	p value (2-tailed)			.568

Table 3. SPSS output for all the data given in Table 1.

ANOVA^b

Model Summary ^b				
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.978 ^a	.957	.947	5.320

a. Predictors: (Constant), Type of athlete, Activity, Exercise intensity

b. Dependent Variable: Heart rate

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	8767.734	3	2922.578	103.254	.000 ^a
	Residual	396.266	14	28.305		
	Total	9164.000	17			

a. Predictors: (Constant), Type of athlete, Activity, Exercise intensity

b. Dependent Variable: Heart rate

Coefficients^a

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B		Collinearity Statistics
		B	Std. Error	Beta			Lower Bound	Upper Bound	VIF
1	(Constant)	.519	9.677		.054	.958	-20.236	21.274	
	Exercise intensity	3.271	1.436	.344	2.278	.039	.191	6.352	7.369
	Activity	9.061	3.328	.328	2.723	.017	1.923	16.199	4.695
	Type of athlete	45.572	5.822	.952	7.827	.000	33.084	58.059	4.790

a. Dependent Variable: Heart rate

gives $r = -0.043$ ($P = 0.867$). That's right, like the line, the relationship is slightly negative. How can this be? Well, if we examine the scatter plot you will notice that there are two clusters of points – and these clusters correspond to the two types of athlete (couch potatoes, upper left; elite, lower right). For bivariate correlation and regression we have here a problem known as *heterogeneity of subsamples*, which would invalidate the analysis. However, if we include the type of athlete, and for good measure the specified activity, into a multiple regression analysis, then we can examine the effects of more than one IV on the DV heart rate. What we see in the plot is that within each cluster there is a clear positive relationship between heart rate and exercise intensity. However, elite athletes have lower heart rates and can work the exercise machine harder. So the apparent negative relationship between heart rate and exercise intensity is due to including two different (heterogeneous) types of athlete in our sample. The R^2 statistic measures how much variability is explained by the relationship between the variables, and here it is negligible at 0.2% (Fig. 1). We need to improve our analysis...

There are three general ways of performing a multiple regression:

standard, sequential (hierarchical) and statistical (stepwise). Here, for simplicity, we will use standard multiple regression, entering all IVs into the analysis simultaneously. All statistical packages will do the analysis, and I will use SPSS (also known as PASW) to illustrate. The output, with various options selected, looks something like Table 3.

SPSS provides a lot of information, but I am going to concentrate only on the essentials. The overall relationship is statistically significant now (see Table 3, ANOVA box) with $P < 0.001$, and the R^2 has dramatically improved to 95.7% (Table 3, Model summary). In the Coefficients box you can see that each of the IVs is now statistically significant ($P < 0.05$), and reassuringly, there is now a positive relationship between heart rate and exercise intensity (unstandardized coefficient, B). The coefficient for type of athlete is large and positive, and represents the large 'step' difference between elite athletes and couch potatoes (coded 0 and 1, respectively). Just like with simple regression we write out the equation, here it would be:

$$\text{Heart rate} = 0.519 + 3.271(\text{Exercise intensity}) + 9.061(\text{Activity}) + 45.572(\text{Type of athlete})$$

What multiple regression does is to calculate the optimal relationship between a combination of predictor IVs and the DV (by minimizing the squared residuals). Each variable's coefficient in the equation tells us how much the DV changes for each unit increase of that IV, while keeping all other IVs constant. Saying an IV is a 'predictor' does not mean that it has a causal relationship with the DV.

Regression analyses are characterised by numerous diagnostic tests. Initially these appear to be tedious formalities; however, with time and experience their usefulness and importance is increasingly valued. One such diagnostic is the *collinearity* (aka *multicollinearity*) statistics given in the last column of the Coefficients box. VIF stands for variance inflation factor, and informs us that the standard errors for the variable coefficients are inflated by between 4.695 and 7.369 times. An alternative statistic usually given is the *tolerance* which is merely the reciprocal of the VIF. Inflation of standard errors indicates instability of the regression equation, and arises because two or more IVs are strongly correlated (+ve or -ve) with each other. A rule of thumb is that you should be very concerned if there is a $VIF > 10$ (or $\text{tolerance} < 0.1$), and act to remove

Table 4. SPSS output for the data in Table 1, with Activity omitted.

ANOVA^b

Model Summary ^b					ANOVA ^b					
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Model	Sum of Squares	df	Mean Square	F	Sig.
1	.966 ^a	.934	.925	6.357	1 Regression	8557.915	2	4278.957	105.900	.000 ^a
					Residual	606.085	15	40.406		
					Total	9164.000	17			

a. Predictors: (Constant), Type of athlete, Exercise intensity

b. Dependent Variable: Heart rate

a. Predictors: (Constant), Type of athlete, Exercise intensity

b. Dependent Variable: Heart rate

Coefficients^a

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B		Collinearity Statistics
		B	Std. Error	Beta			Lower Bound	Upper Bound	VIF
1	(Constant)	-17.571	8.406		-2.090	.054	-35.488	.346	
	Exercise intensity	6.731	.800	.707	8.410	.000	5.025	8.436	1.603
	Type of athlete	58.502	4.024	1.222	14.539	.000	49.926	67.079	1.603

a. Dependent Variable: Heart rate

one or more IVs. We should be a bit concerned about the 7.369 associated with exercise intensity. Since we are particularly interested in this variable as a predictor of heart rate we should look at other IVs for removal. Clearly, type of athlete is also crucial (that's how we got into doing the multiple regression to avoid heterogeneous subsamples), so we could consider removing the type of activity. It is quite strongly correlated with exercise intensity ($r = 0.603$, Table 2); moreover, its standardized coefficient at 0.328 is the smallest – which means it is the weakest among the three predictors. Although it is often easy to find statistical reasons to include or remove IVs, the best reasons come from your understanding of the importance of particular variables for

the purpose of the analysis. Variables that are of theoretical importance, even if not statistically significant, should still be included in a multiple regression. Let us say here, for illustrative purposes, that we are primarily interested in exercise intensity and so remove the type of activity variable. The SPSS output is given in Table 4.

You can see that R^2 is still very large at 93.4% (Table 4, Model Summary box). The VIFs are now much lower, giving narrower 95% confidence intervals for the variable Bs (Coefficients box). In addition, the standardized coefficients (Betas) are higher and more statistically significant (both $P < 0.001$). Our equation is now:

$$\text{Heart rate} = -17.571 + 6.731(\text{Exercise intensity}) + 58.502(\text{Type of athlete})$$

We could predict the heart rate of a couch potato doing moderate exercise (say intensity of 9) as:

$$\text{Heart rate} = -17.571 + 6.731(9) + 58.502(1) = 101.510$$

With one IV, the relationship with the DV is two dimensional about a fitted line; with two IVs we can visualise the fit in three dimensions with data points scattered about a plane. With three or more IVs the points are scattered in hyperspace. In our example, two clusters of points occur at different places about a plane, each cluster determined by the type of athlete (see Fig. 2).

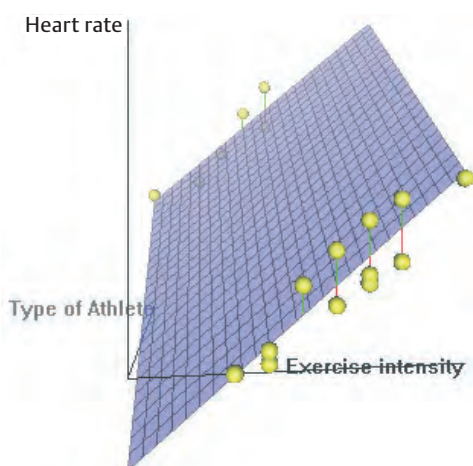


Figure 2. 3-D plot of the variables.

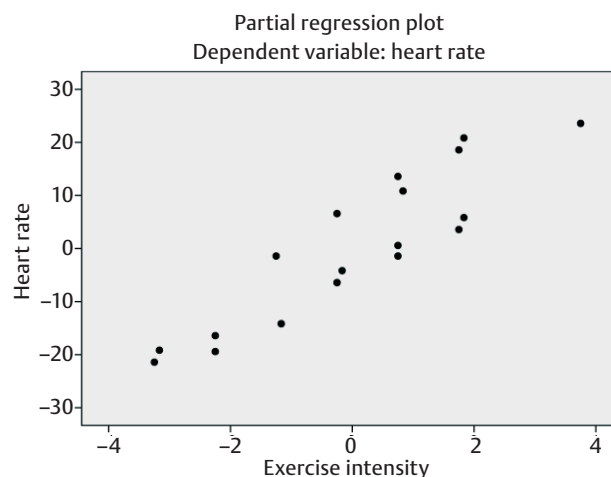


Figure 3. Partial regression plot. If the effect of different types of athlete is kept constant, then we can see that there is a clear positive linear relationship between heart rate and exercise intensity here. Scales are centred on the means.

In order to see the relationship of an individual IV and DV it is possible to do a *partial regression plot*. Of particular interest to us is intensity of exercise as a predictor of heart rate (see Fig. 3). Here we see a cigar-shaped and clear positive relationship between these variables (as we had expected).

Multiple regression is a useful general technique for analysing data where the DV (aka *outcome* or *criterion* variable) is associated with more than one IV (aka *explanatory* or *predictor* variable). It can handle continuous and dichotomous IVs (and indeed the DV can also be dichotomous, as in *logistic regression*). Regression can be done instead of ANOVA (by dummy variable coding the different levels of a factor), but ANOVA cannot necessarily be done using regression data if one or more variables are continuous (though can be done by converting to e.g. low/med/high – but with loss of information). ANOVA is a restricted form of regression. Actually our particular example could have been analysed in a between-participants ANOVA, entering type of athlete as a fixed factor and exercise intensity as a covariate, but it would not normally have produced the coefficients used to construct the equation.

Regression can include the outputs from other analyses. A good example is the use of output scores from a principal components analysis (PCA, see Patricia de Winter's article in the previous issue, **PN79**) to reduce the dimensionality of the variables used. In the above hypothetical study it may have been possible to derive a variable 'fitness' (known as a *latent* variable) if we had administered a questionnaire with numerous questions about participants' sporting activities (how often they train, how long, what type of activity, etc. etc.). The factor scores for the relevant component would then be entered as a variable into the regression analysis. More generally, if we had problems of collinearity among a set of variables

in our regression analysis, we could carry out a PCA on those variables, which would reduce them to a subset of uncorrelated factors. The factor scores would then be used in a regression analysis (however, we would need to be sure what each factor represents).

In practice, you should carefully choose which variables to enter, rather than just enter them all. Sometimes attempts are made to find the best equation by entering as many IVs as possible, regardless of their meaning. Unfortunately this is encouraged by stepwise procedures, and should be avoided, except perhaps for exploratory analyses. It is important to stress that for an accurate regression equation, all *relevant* IVs with respect to DV changes must be included in an analysis. Imagine if we had not included the type of athlete variable in our example (and had not recorded it), we would have been unable to interpret our data. If there are more IVs than cases then the regression equation predicts precisely the DV values. We could have included sex, type of sport, age, height, weight, health status, etc. etc. as predictors. This would lead to a better fit to the particular sample data, but paradoxically leads to a less useful result because of *overfitting* to the idiosyncrasies of our particular sample. This means that the results of our analysis might not be readily applicable to other data selected from the same population, i.e. there is poor generalization. One way to check how 'good' the regression equation is, is to apply cross-validation to the data. Here, a regression equation developed from a randomly selected large subset of the data is then used to predict scores from the remaining data. The predicted and actual scores are correlated, and the R^2 compared with the initial R^2 from the larger subset. We would expect the former value to be similar though slightly lower than the latter.

As mentioned above, regression analyses come with numerous

diagnostics. In order to check assumptions for the analysis, it is useful to look at residuals for unexplained variability, outliers or non-linearity. A plot of standardized residuals against standardized predicted values should show a random cloud of points. A departure from that pattern suggests a bad fit. It may indicate that an important IV is missing. Alternatively, a clear pattern among the points, such as a curved wave or increasing spread (funnel shaped) with increasing predicted values, could indicate that an IV or DV should be transformed (e.g. square and log transform, respectively). In some situations it may be appropriate to look at an interaction between IVs, by multiplying two or more of them together, and entering the resultant product, along with the individual IVs, into the analysis. Non-independence of residuals indicates another variable is in play (e.g. the order in which the data were collected), and needs to be taken into account. The residuals should also be normally distributed. An important assumption is linearity. If a factor with m levels is non-linear with respect to the DV, it can be converted into $m - 1$ *dummy* variables (coding each with 0 and 1), ensuring linearity since a straight line always connects between the two points $0, y_1$ and $1, y_2$. A number of diagnostics help detect outliers which might exert excessive leverage within the equation.

Finally, it is necessary to say something about sample size. Our fabricated example was clearly deficient. Generally, with medium-sized effects, you will need at least 50 participants + $(8 \times \text{no. of IVs})$. So in our example we would need $50 + (3 \times 8) = 74$. Otherwise, the more the better.

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Lymphatic vessels – absorptive sumps or leaky pumps?

Lymphatic vessels, the absorptive vessels of the body, are responsible for catching fluid filtered from capillaries and returning it to the bloodstream, a process necessary for life. A commonly espoused hypothesis for their success is that the lymphatic vessel wall is impermeable to solute that has already entered from the tissue through the initial lymphatics. Contrary to this textbook view, recent studies demonstrate that lymphatic vessels are surprisingly leaky.

All blood microvessels leak proteins, sugars, gases and water into the tissues, be they arterioles, capillaries or venules. By virtue of their resemblance to these blood vessels, shouldn't lymphatic vessels leak solute and water as well? In fact, this thought process led to studies examining protein loss from the lymphatic vasculature by Mayerson *et al.* (1962), when they infused canine leg lymphatics with radiolabelled albumin and collected lymph simultaneously from the thoracic duct (where the lymphatic vasculature empties into the blood). As Fig.1 depicts, Mayerson *et al.* detected less than 3% of the infused albumin in blood; from this they concluded that the lymphatic circulation was virtually impermeable to albumin. Probably as a consequence, over the next half-century many assumed that these vessels were impermeable to protein, otherwise their contents would leak right back out into the tissue thereby negating their primary function.

Less emphasized, however, were their studies demonstrating that smaller molecules crossed the lymphatic wall so rapidly that they equilibrated with the tissues and blood. In this work, the rate at which molecules were lost across the lymphatic vessel wall decreased as the molecular size increased, a phenotype discovered earlier for blood microvessels (Mayerson *et al.* 1962).

Unfortunately, measuring the total amount of protein crossing lymphatic vessels *per se* is not very informative because it does not quantify the permeability of a vessel to a molecule. 'Permeability' is a coefficient describing the ease with which molecules traverse a vessel wall, and is more accurate because it



Virginia Huxley and Joshua Scallan

is a measure of the amount of solute that moves across a vessel segment over time (flux) when both its surface area and the concentration gradient are known (and unchanging). Accounting for such variables may seem trivial at first, but increasing the vessel surface area or concentration gradient will increase the flux of molecules

moving across the lymphatic wall, making the vessel appear *false* as more or less 'permeable'. Discussing solute movement in terms of permeability also enables direct comparison of data from vessels separated spatially or temporally.

A newer technique borrowed from those studying blood microvessels, where fluorescently labelled proteins are perfused through vessel segments isolated from tissue, facilitates the measurement of lymphatic vessel permeability. While the data are sparse, the dependence of solute movement on molecular size has been confirmed for the lymphatics (Ono *et al.* 2005; Price *et al.* 2008). The latter study (Price *et al.* 2008), in

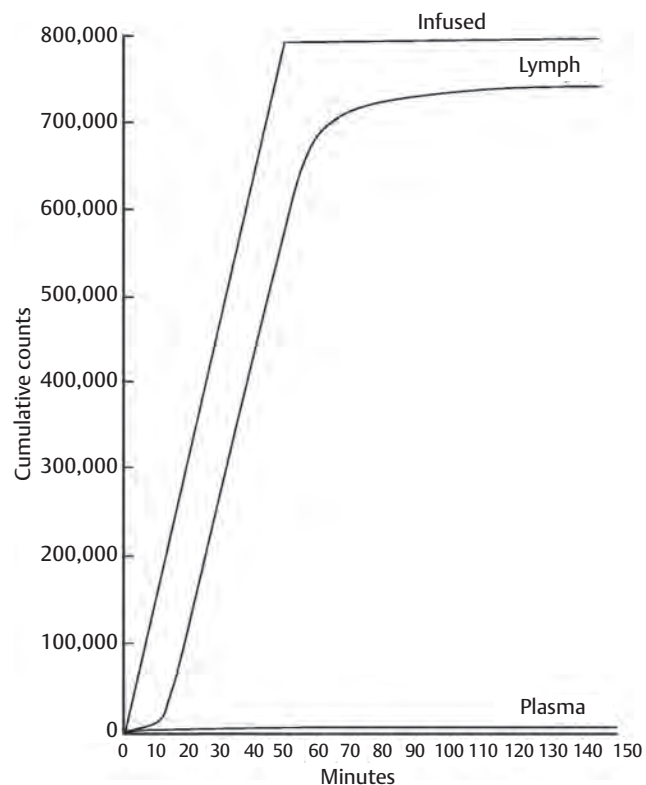


Figure 1. After infusion of radiolabelled albumin into a lymphatic duct of a canine leg, the cumulative radioactivity (counts) was detected in thoracic duct lymph and plasma over time. The conclusions from this work were that almost all of the albumin was retained by the lymphatic vessels. Please see the text for a more thorough discussion of this interpretation. Redrawn from Mayerson *et al.* (1962) with permission.

which lymphatic endothelial cells (LECs) were grown inside artificial tubes made of collagen, reported absolute permeability values that, for comparison, were approximately 10 times that measured for venules

(Scallan & Huxley, 2010). Whether it is justifiable to make conclusions of *in vivo* lymphatic solute transport from an artificial system lacking several barrier components is debatable.

One group to date has assessed lymphatic permeability *in vivo* by cannulation and perfusion with fluorescently labelled albumin (Scallan & Huxley, 2010) to test the hypothesis that lymphatic vessels

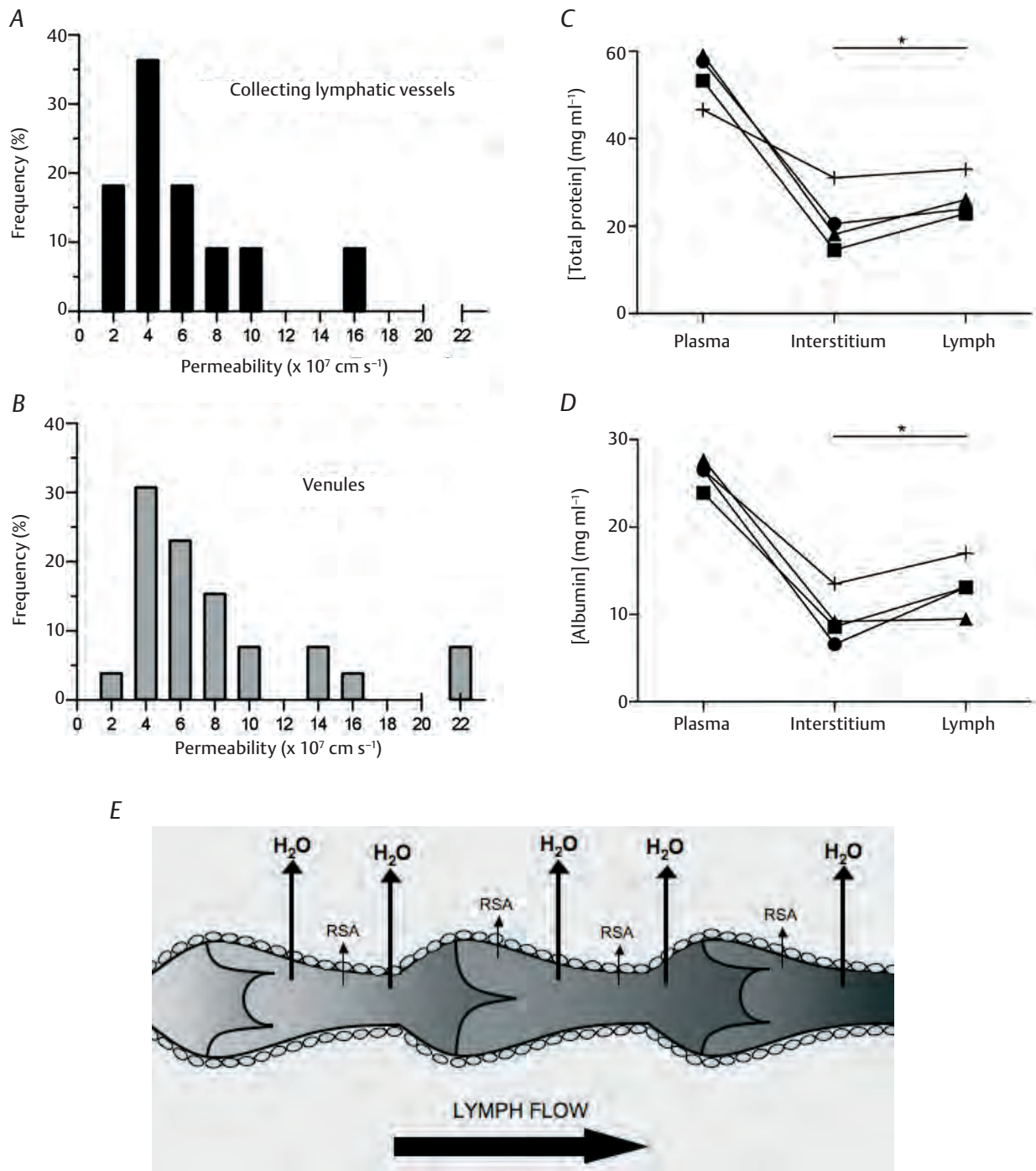


Figure 2. The albumin permeability of collecting lymphatic vessels mimics that of the venules. *A* and *B*, when the frequencies of individual measures of vessel permeability are plotted for both vessel types, neither are normal distributions. Further, the medians (or means) of each group do not differ. However, this does not provide information about the direction in which the albumin is traveling (i.e. whether it moves into or from the vessel lumen). This was assessed by simultaneous measures of plasma, interstitial, and lymph total protein (*C*) and albumin (*D*) concentrations, which demonstrated that protein is expected to 'leak' from the lymphatic vessel lumen. *E*, an overall schematic of water and albumin movement across the collecting lymphatic vessel barrier. As it was estimated that much more water is lost to the tissues than solute, the contents of the vessel are concentrated (darker shading corresponds to a greater solute concentration). * $P < 0.1$.

containing valves and spontaneously contracting muscle cells (called collecting lymphatics) possess a basal permeability to albumin no different from the venules. Since LECs are derived from cardinal vein endothelium during development (Srinivasan *et al.* 2007), their rationale was that LECs share many genes, and probably functions, with blood endothelium. The study concluded that collecting lymphatic permeability to albumin did not differ from that of venules (Fig. 2). Furthermore, the permeability of initial lymphatics – devoid of valves and muscle cells – was determined to be similar to the LEC tubes with an ~10-fold greater permeability than the venules. Therefore, heterogeneity exists with respect to permeability among the different lymphatic vessel types, the same being true for blood microvessels (e.g. venules and capillaries are leakier than arterioles).

Okay, lymphatic vessels are as permeable as blood microvessels, but where does all this solute go? For vessels, the sum of hydrostatic and osmotic pressures determines whether water and solute movement is directed towards the interstitium (net leak) or towards the vessel lumen (net absorption). Pressure, as well as vessel and tissue protein concentrations, must be measured simultaneously to know these forces. Well established for blood vessels is that water is generally filtered into the interstitium, carrying with it macromolecules such as albumin, which diffuses down its concentration gradient into the tissue. However, no experiments have performed matched measurements of collecting lymphatic, tissue and blood protein concentrations. Scallan & Huxley (2010) not only made these paired measures, but also recorded vessel hydrostatic pressures prior to their experiments. Thus, the data in Fig. 2 demonstrate that collecting lymphatics possess a greater protein concentration in their lumen than in the tissue, favouring diffusion of albumin out of the vessel. Additionally, collecting lymphatics

all maintained hydrostatic pressures well into the positive range, so that one may expect net fluid filtration into the tissue.

Upon reconsideration of their main function – to absorb fluid and protein for return to the blood – these conclusions seem contradictory. How can lymphatic vessels both absorb *and* leak protein-containing fluid? Examining the two lymphatic vessel types provides clues. Initial lymphatics form the entryway into this vasculature; consequently their hydrostatic and osmotic driving forces are low. Collecting lymphatics are larger, downstream contractile vessels possessing greater pressures and driving forces. Therefore, protein absorbed by the initial lymphatics will enter the collecting lymphatics where only a percentage will diffuse into the tissues down a concentration gradient. Reinforcing this conclusion Scallan & Huxley (2010) estimated that: (1) the collecting lymphatics filter more water than protein, effectively concentrating luminal protein and steepening the concentration gradient and (2) solute will be entrained by the filtering water (see Fig. 2).

The field investigating microvessel permeability is small, such that our complete knowledge of lymphatic vessel permeability has been

presented here. Undoubtedly, much remains to be learned about this second circulatory system, but what can be gleaned from the aforementioned experiments demonstrates that the lymphatic vasculature is capable of providing nutrients to tissues in regions where blood vessels are scarce while at the same time regulating fluid homeostasis.

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Electrical synapses synchronize motor output for tadpole swimming

In the vertebrate brain, electrical synapses can synchronize activity in populations of neurons with similar roles. The strength of these synapses is not fixed, however, and may be regulated under different behavioural or developmental circumstances. In hatchling *Xenopus laevis* tadpoles, neighbouring motoneurons controlling the segmented swimming muscles are synchronized by electrical synapses, but as development proceeds coupling is turned down to allow more flexibility in motor output.

Gap junctions provide low resistance paths for the diffusion of ions and small molecules between neighbouring cells. They underlie the electrical synapses that couple neuronal activity in some networks. Until recently the presence of electrical coupling via gap junctions was thought to prevail mainly in invertebrates and at early stages of vertebrate development (Walton & Navarette, 1991), but more recently the presence of electrical synapses in both juvenile and mature networks throughout the vertebrate CNS has significantly increased interest in the role of electrical transmission in neural circuit function.

Shaping the swimming motor programme in hatching *Xenopus* tadpoles

At the time of hatching from their egg membranes (stage 37/38), tadpoles of the South African clawed frog, *Xenopus laevis*, are normally stationary but are able to swim when touched. They propel themselves through the water by generating side-to-side oscillations of the body at frequencies of 10 to 20 Hz. The swimming muscles, or myotomes, are segmented blocks of somitic origin which contract in a precisely coordinated sequence with strict



Clockwise from top left: Hong-Yan Zhang, Bill Heitler, Keith Sillar and Wen-Chang Li.

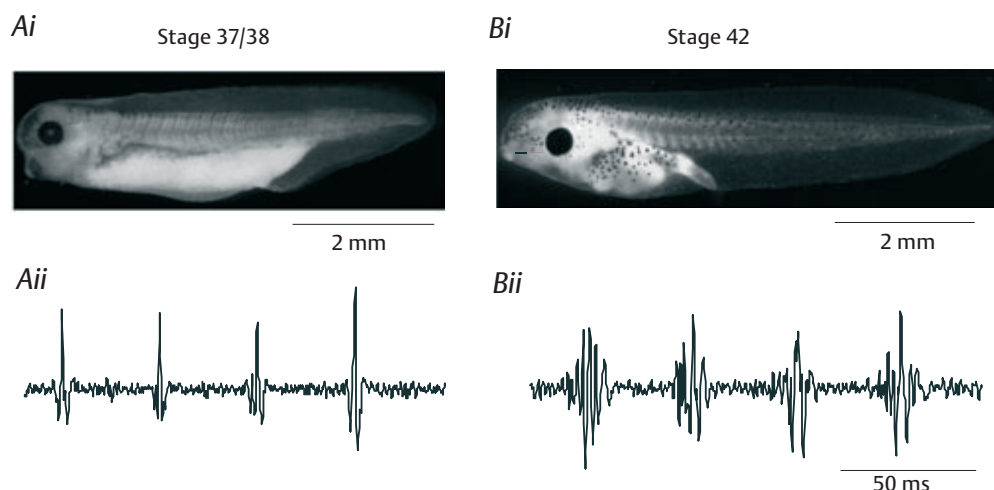
alternation between the left and right sides, and a head-to-tail propagation with a brief delay between adjacent segments. Intracellular recordings from myotomal motoneurons during swimming show that the population supplying a given muscle segment all fire synchronously, and that each motoneuron normally fires just a single action potential per cycle. This results in bursts of ventral root discharge which, when recorded with extracellular suction electrodes, last only about 5 ms (Fig. 1A). The majority of the population of 12 to 15

motoneurons per segment discharge on almost every cycle of swimming, irrespective of the swimming frequency, constraining motor output flexibility at this early stage of development.

The motor system of *Xenopus laevis* tadpoles changes its output dramatically in just 24 hours after hatching, with a large increase in the duration of ventral root bursts (stage 42, Fig. 1B). This rapid developmental change presents an excellent opportunity to study the function of electrical coupling in a simple, developing model system.

The presence of electrical connections between neighbouring motoneurons at stage 37/38 (Perrins & Roberts, 1995a,b) suggests a causal role for gap junctions in the synchronization of activity, since a change in transmembrane voltage in one member of an electrically coupled syncytium will 'drag' the membrane potentials of its neighbours, with minimal delay, in the same direction. Furthermore, since recent patch clamp recordings of the same motoneurons have shown that when depolarized by injected current they are capable of firing multiple action potentials (Zhang *et al.* 2009), the fact that they

Figure 1. Two developmental stages of *Xenopus laevis* tadpole and examples of their ventral root activity. *Ai*, stage 37/38 tadpole around the time of hatching; *Bi*, after a further 24 hours of development, the stage 42 *Xenopus* larva is ~40% longer and about to become free swimming; *Aii* and *Bii*, examples of swimming bursts at stage 37/38 and 42, respectively.



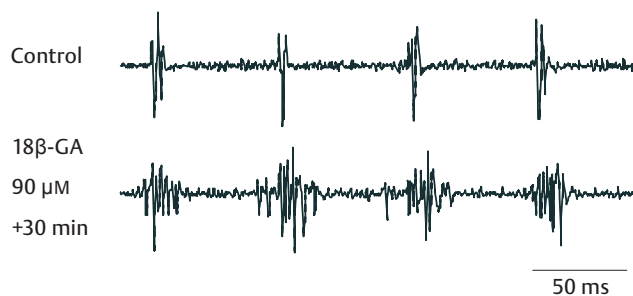


Figure 2. Effects of gap junction blocker, 18 β -GA (90 μ M) on ventral root bursts during fictive swimming.

only fire once per swim cycle might also be partially due to electrical coupling. It is not known if there is a particular advantage to the embryo of synchronizing and limiting firing in motoneurons serving each myotome, but perhaps this optimizes muscle contraction.

Electrical coupling in the spinal cord appears to be limited to within the same neuron classes: motoneuron–motoneuron (e.g. *Xenopus* tadpole, Perrins & Roberts, 1995a), or interneuron–interneuron interactions (e.g. neonatal mouse, Hinckley & Ziskind-Conhaim, 2006). Recently it has been established that a population of excitatory interneurons in the tadpole swimming network, called dINs, also form an electrically coupled network (Li *et al.* 2009). These glutamatergic interneurons are critical for the maintenance of the swimming rhythm; rostrally located dINs form positive feedback connections amongst each other such that they drive the spinal swimming rhythm for many tens or hundreds of consecutive cycles (Li *et al.* 2006). This suggested that the electrical synapses amongst them might be

important in sustaining rhythmic locomotor activity once it has started.

Pharmacology of gap junctions and electrical synapses

Two perennial problems in studying the role of electrical synapses in neural network activity have been: (i) the difficulty in making paired recordings from coupled neurons; and (ii) the paucity of specific drugs that block gap junctions. Although certain pharmacological reagents that block gap junctions have been available for a long time, they have a reputation for being non-specific and capricious. The prevalence of electrical coupling between the dINs, pairs of which can be recorded simultaneously with two patch electrodes, provided an excellent opportunity to test the specificity of some commercially available gap junction blockers (Li *et al.* 2009). When applied at concentrations sufficient to block electrical coupling between dINs, all except one drug, 18 β -glycyrrhetic acid (18 β -GA), had serious unwanted side effects. 18 β -GA was therefore the drug of choice for further detailed

investigation into the consequences of gap junction blockade.

The most striking effect of 18 β -GA on the ventral root bursts was to cause a gradual increase in duration from *circa* 5 ms up to 20 ms (Fig. 2), similar to the increase that occurs naturally by stage 42 of development (Fig. 1Aii and Bii).

The effect was dependent on the concentration of blocker applied, suggesting that the gradual removal of the influence of electrical coupling allowed motoneuron firing in each cycle to de-synchronize. Two plausible and non-exclusive consequences of gap junction blockage might account for this change. First, the motoneuron population might de-synchronize, and second, individual motoneurons might start to fire multiple spikes per cycle. Patch clamp recordings from motoneurons confirmed the former but not the latter hypothesis (Zhang *et al.* 2009). The motoneurons still only fired a single spike per cycle, but the temporal coordination of their firing relative to each other was disrupted, producing a de-synchronized ventral root burst (Fig. 3).

An additional dose-dependent effect of the gap junction blocker was a reduction in the duration of the swim episode, an effect not readily explicable at the level of the motoneurons. The most likely reason for this effect is that the reduced coupling between dINs reduces the firing level of their population, thus weakening the rhythm-generating mechanism (Fig. 4), which is based on positive feedback among dINs (Li *et al.* 2009).

What happens during development?

Gap junction coupling at the time of hatching therefore synchronizes the single spiking of motoneurons in each cycle. However, just one day later in development *Xenopus* larvae generate a very different motor pattern in which the duration of each ventral root burst increases to around 20 ms (Fig. 1Aii and Bii), remarkably similar to the effect of 18 β -GA on embryo swimming bursts (Fig. 2). This led to the hypothesis

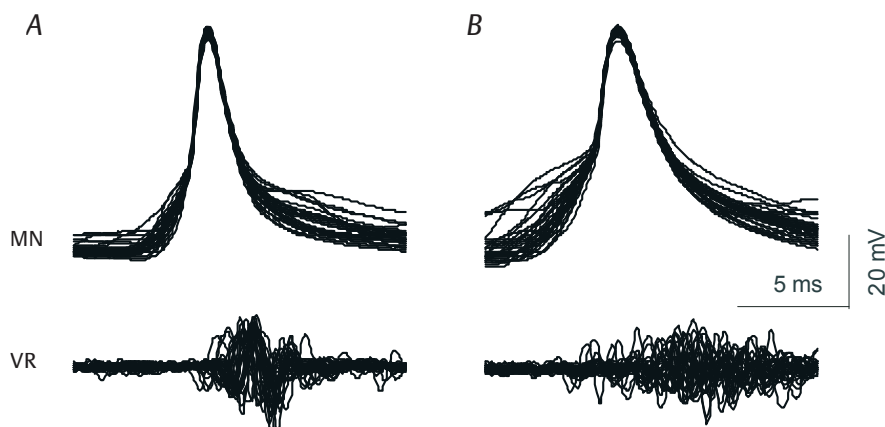


Figure 3. Superimposed motoneuron (MN) spikes and ventral root (VR) bursts aligned to MN spike peaks. A, control; B, 30 min after applying 18 β -GA. Note increase in spike width in 18 β -GA (Zhang *et al.* 2009).

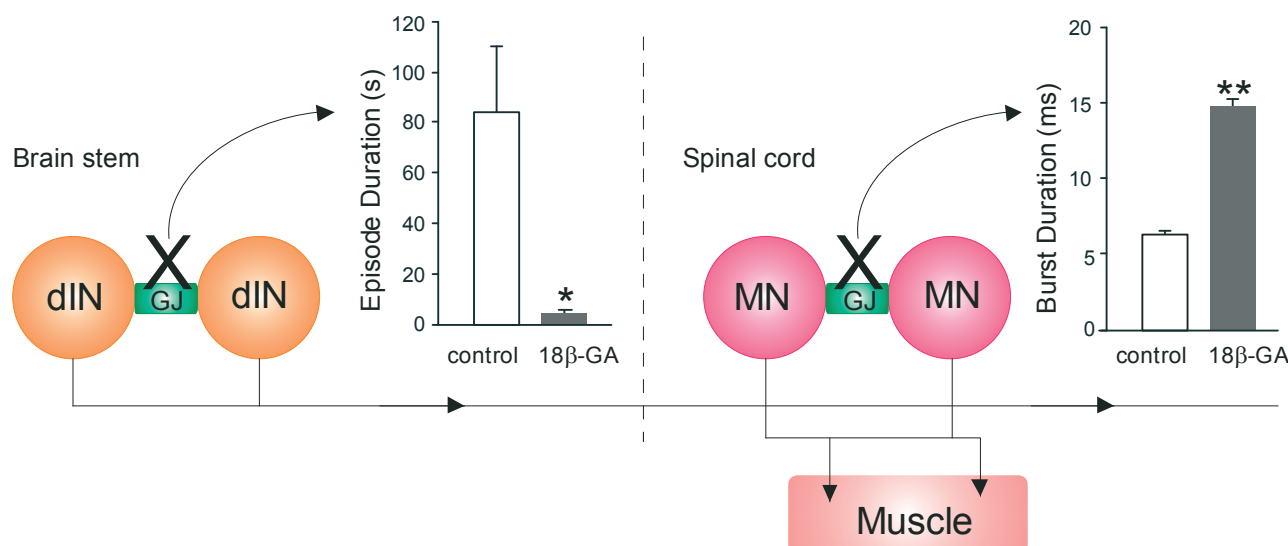


Figure 4. Schematic of 18β -GA blockade of gap junctions (GJ) in the motor network of *Xenopus* tadpoles. Blocking gap junctions between dINs and motoneurons (MN) leads to shorter swimming episodes and longer burst durations, respectively. * $P < 0.05$; ** $P < 0.01$.

that during development there is a reduction in electrical coupling, allowing motoneurons to escape from synchrony. The outcome is a motor pattern that is inherently more flexible because it is no longer constrained by the synchronizing influence of gap junctions.

We tested this hypothesis by applying the gap junction blocker at the highest concentration tested at the hatching stage to larval stage 42 tadpoles and found that the drug had no effect on either ventral root burst or swim episode durations. This suggests that gap junctions no longer play a significant role in coordinating motoneuron activity or sustaining larval swimming and that the effects on the hatching stage are indeed a direct result of the drug's effect on electrical coupling. A further implication of these findings is that the electrical coupling between motoneurons does not play a crucial role in the developmental transition from single to multiple spikes per cycle in individual motoneurons because gap junction block at the hatching stage does not affect the neurons' single spike per cycle pattern during swimming.

Motor system development – cause or effect of gap junctions?

Perhaps the simplest explanation for the change in the motor output pattern during the development of the tadpole swimming system is

that the gene for electrical synapse proteins, presumably connexins of some sort, is turned off around the time of hatching, allowing motoneurons to de-synchronize their firing. A more complex hypothesis, which still needs to be tested, is that the gap junctions are still present but the coupling strength is merely turned down, for example by an intrinsic modulator, so that they may be available at a later date for some unknown function. There is good evidence in other systems that electrical synapses are subject to neuromodulation, for example by biogenic amines like dopamine or serotonin (Lasater & Dowling, 1985; Roerig & Sutor, 1996). The developmental transition in tadpole swimming from a simple, brief ventral root burst to a more robust and flexible burst in larvae is under serotonergic control from the raphe nucleus whose projections invade the spinal cord over precisely the same period of development. Therefore it is conceivable that the growth of raphe axons and their release of serotonin regulates the developmental expression of swimming output by decreasing gap junction coupling between motoneurons.

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HIT to get fit: metabolic adaptations to low-volume high-intensity interval training

Low-volume high-intensity interval training (HIT) induces metabolic adaptations that resemble traditional endurance training despite a reduced total exercise volume and time commitment. HIT may therefore represent a time-efficient exercise strategy to improve health. It remains to be determined whether this form of training elicits all of the benefits associated with high-volume continuous exercise, and whether low-volume HIT can be safely and effectively implemented in the general population and persons with chronic diseases.

Regular endurance exercise training induces numerous adaptations that enhance functional performance, improve health and reduce the risk for chronic disease. While the physiological changes are complex and involve multiple organ systems, metabolic adaptations in skeletal muscle play a critical role in the beneficial effects of endurance training. In particular, exercise-induced increases in muscle oxidative and glucose transport capacities are believed to contribute to the reduced risk of diseases such as insulin resistance and type 2 diabetes (T2D). Recent studies have demonstrated that low-volume, high-intensity interval training (HIT) induces numerous metabolic and performance adaptations that are remarkably similar to traditional endurance training despite a lower total exercise volume and training time commitment (Gibala & McGee, 2008). Given that 'lack of time' is the most commonly cited barrier to regular exercise participation, low-volume HIT may represent an attractive alternative for promoting beneficial adaptations in the general population.

What is HIT?

HIT is characterized by brief repeated 'bursts' of vigorous exercise interspersed with periods of rest or low-intensity exercise for recovery. The training impulse (i.e. interval intensity, duration and number) is infinitely variable, with single efforts lasting from a few seconds up to several minutes. The primary focus of our laboratory in recent years has been on the effects of low-volume HIT. In this type of HIT, the interval training intensity is very high yet the total amount of



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exercise performed during training is purposefully low. Our HIT training model was the Wingate test, which consists of a 30 s 'all out' cycling effort against a standardized resistance. In a typical training session, subjects completed four to six Wingate tests, interspersed with 4 min of rest in between bouts. Thus, training sessions consisted of only 2–3 min of maximal exercise and required a training time commitment of ~20–25 min. Six sessions of this low-volume HIT protocol over 2 weeks is a potent stimulus to increase muscle oxidative

capacity and enhance endurance performance (Fig. 1) (Gibala *et al.* 2006). This same protocol was also recently reported to improve insulin sensitivity, as shown by a study in press in *The Journal of Physiology* that applied the hyperinsulinaemic-euglycaemic clamp technique in overweight men (Richards *et al.* 2010). These findings highlight the potential for low-volume HIT to improve metabolic health.

The need for a more practical model of HIT

Wingate cycling tests require a specialized cycle ergometer and the 'all-out' maximal effort necessitates an extremely high level of subject motivation. Therefore, the aforementioned low-volume HIT protocols are very demanding and may not be safe or practical to implement in the general population. In a recent publication in *The Journal of Physiology* (Little *et*

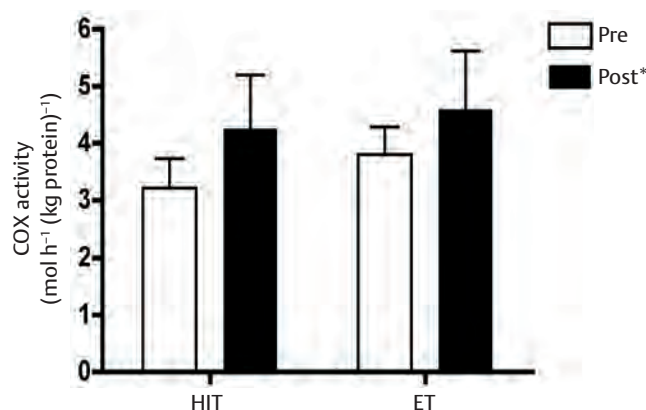


Figure 1. Low-volume high-intensity interval training (HIT) induces metabolic adaptations in skeletal muscle that are comparable to endurance training (ET). Maximal activity of the mitochondrial enzyme cytochrome c oxidase (COX) measured in skeletal muscle biopsy samples taken before (Pre) and after (Post) 2 weeks of Wingate-based HIT and traditional ET. Total training volume and time commitment were ~90% and ~75% lower, respectively, in HIT compared to ET. * $P < 0.05$ vs. Pre. Adapted from Fig. 2 in Gibala *et al.* (2006).

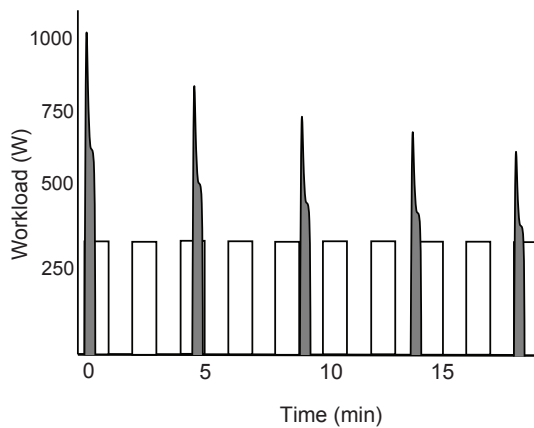


Figure 2. Schematic representation of two protocols of low-volume high-intensity interval training (HIT). The power output (y-axis) and time (x-axis) required for a single session of low-volume high-intensity interval training (HIT) are depicted in this diagram. The gray bars illustrate an example power output during five repeated 30 s all-out cycling sprints with 4 min rest in between during a typical low-volume Wingate-based HIT session. The open bars illustrate an example power output during 10 x 1 min intervals at $\sim 100\%$ maximal oxygen uptake ($\dot{V}_{O_{2peak}}$) during the more practical model of low-volume HIT used in our recent publication.

et al. 2010), we evaluated whether a more practical model of low-volume HIT could elicit metabolic and performance adaptations similar to our previous Wingate-based HIT studies. The practical model was designed to keep total training time commitment relatively low (requiring approximately 1 h per week), decrease the absolute intensity of the intervals, and be performed on a standard stationary bicycle similar to that found in fitness clubs or home gyms. The modified HIT protocol involved 8–12 x 1-min intervals at an intensity that corresponded to $\sim 100\%$ peak oxygen uptake with 75 s rest periods in between

(Fig. 2). While still a demanding form of exercise, the absolute work intensity corresponded to less than half of that achieved during an all-out Wingate test. Despite these modifications, the training was still ‘time efficient’ in that only ~ 10 min of exercise was performed over a 15–25 min period during each training session.

Six sessions of this modified HIT protocol over 2 weeks was a sufficient stimulus to increase functional exercise performance, assessed using cycling time trials, and enhance skeletal muscle oxidative capacity, assessed by

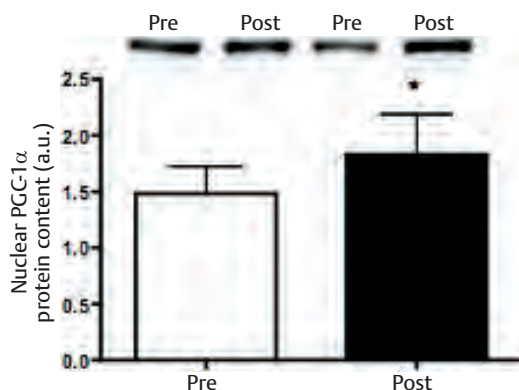


Figure 3. Low-volume high-intensity interval training (HIT) increases nuclear PGC-1 α protein content. Relative protein content of PGC-1 α measured in nuclear fractions prepared from human skeletal muscle biopsy samples obtained before (Pre) and after (Post) 2 weeks of practical low-volume HIT. Representative Western blots for 2 subjects are shown. * $P < 0.05$. Adapted from Fig. 4 in Little *et al.* (2010).

measuring the protein content and maximal activity of selected mitochondrial enzymes. Skeletal muscle glucose transporter (GLUT4) content and resting muscle glycogen content were also increased following training. These latter findings provide additional support for the potential benefits of low-volume HIT for improving glycaemic regulation. We also examined the effects of training on several proteins that are implicated in regulating the muscle adaptive response. Training increased the content of the transcriptional regulatory protein peroxisome proliferator-activated receptor γ co-activator (PGC)-1 α measured in nuclear fractions (Fig. 3) yet total PGC-1 α appeared unchanged. PGC-1 α has emerged as an important regulator of mitochondrial and metabolic gene expression by virtue of its ability to co-activate numerous transcription factors in the nucleus. The increase in nuclear PGC-1 α suggests that low-volume HIT increases the activation of this critical regulatory protein. Evidence suggests that PGC-1 α activation is reduced in conditions of obesity, insulin resistance, T2D and ageing. The ability of low-volume HIT to increase PGC-1 α activation provides mechanistic support for the potential health benefits of this type of time-efficient exercise training.

Future directions

Despite evidence for low-volume HIT to promote metabolic adaptations linked with improved health, more research is required to determine whether HIT elicits all of the benefits associated with traditional endurance training. An accumulating body of research indicates that interval-based exercise induces superior cardiovascular benefits compared with continuous aerobic training matched for total work (Wisloff *et al.* 2009). Whether low-volume HIT is of similar benefit to cardiovascular health requires further investigation. In addition, most of the low-volume HIT research published to date has involved

relatively short-term training protocols (up to 6 weeks) and additional studies are warranted to examine the long-term adaptations to this type of training. Finally, it remains to be determined whether our practical low-volume HIT model (Little *et al.* 2010) can be implemented in a wide variety of populations. Encouragingly, recent unpublished work from our laboratory suggests that this HIT model is well-tolerated and can improve muscle oxidative capacity and markers of glycaemic control in sedentary, middle-aged adults as well as individuals with T2D. Low-volume HIT may therefore represent an attractive time-efficient exercise alternative for reducing the risk of metabolic disease.

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Newly elected Fellow of the Royal Society for 2010

Roger Clayton Hardie FRS

We are pleased to announce that Roger Hardie has been elected a Fellow of the Royal Society. Roger is Professor of Cellular Neuroscience, Department of Physiology Development and Neuroscience, Cambridge University and became a Member of The Society in 2008.

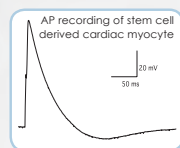
Together with Baruch Minke, Roger demonstrated that the *trp* gene encodes the light-sensitive channels in *Drosophila* photoreceptors. This launched the TRP channel field, now a major part of calcium signalling and a focus of medical research. His subsequent investigations using the prototypical dTRP channels have been marked by elegant technological innovations, leading to groundbreaking and novel insights into the complex regulation of this class of channels by calcium and by lipid messengers.

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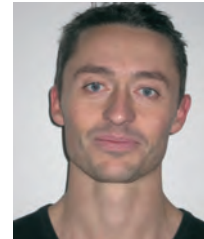
Can growth hormone strengthen the connective tissue of muscle and tendon?

Growth hormone (GH) doping is motivated by its presumed muscle anabolic properties, but paradoxically human studies show no effect of GH supplementation on contractile muscle protein synthesis. We demonstrated that GH supplementation increases connective tissue collagen synthesis in human muscle and tendon, without affecting muscle myofibrillar protein synthesis. Thus, GH supplementation potentially reinforces the supporting connective tissue and could make muscles and tendons less prone to injuries.

Growth hormone and collagen protein

The major role of connective tissue in muscle and tendon is to provide a matrix for the transmission of force from the individual muscle fibres to the bone. Collagen is the primary tensile-resistant protein in musculo-tendinous connective tissue and is a key determinant of tendon

strength. In relation to overuse and traumatic muscle and tendon injuries, collagen is inevitably damaged, and recovery depends on the *de novo* synthesis of collagen. Mechanical loading, as well as several different growth factors, including growth hormone (GH) and insulin-like growth factor-I (IGF-I), appears to have the



Simon Doessing (left) and Michael Kjaer.

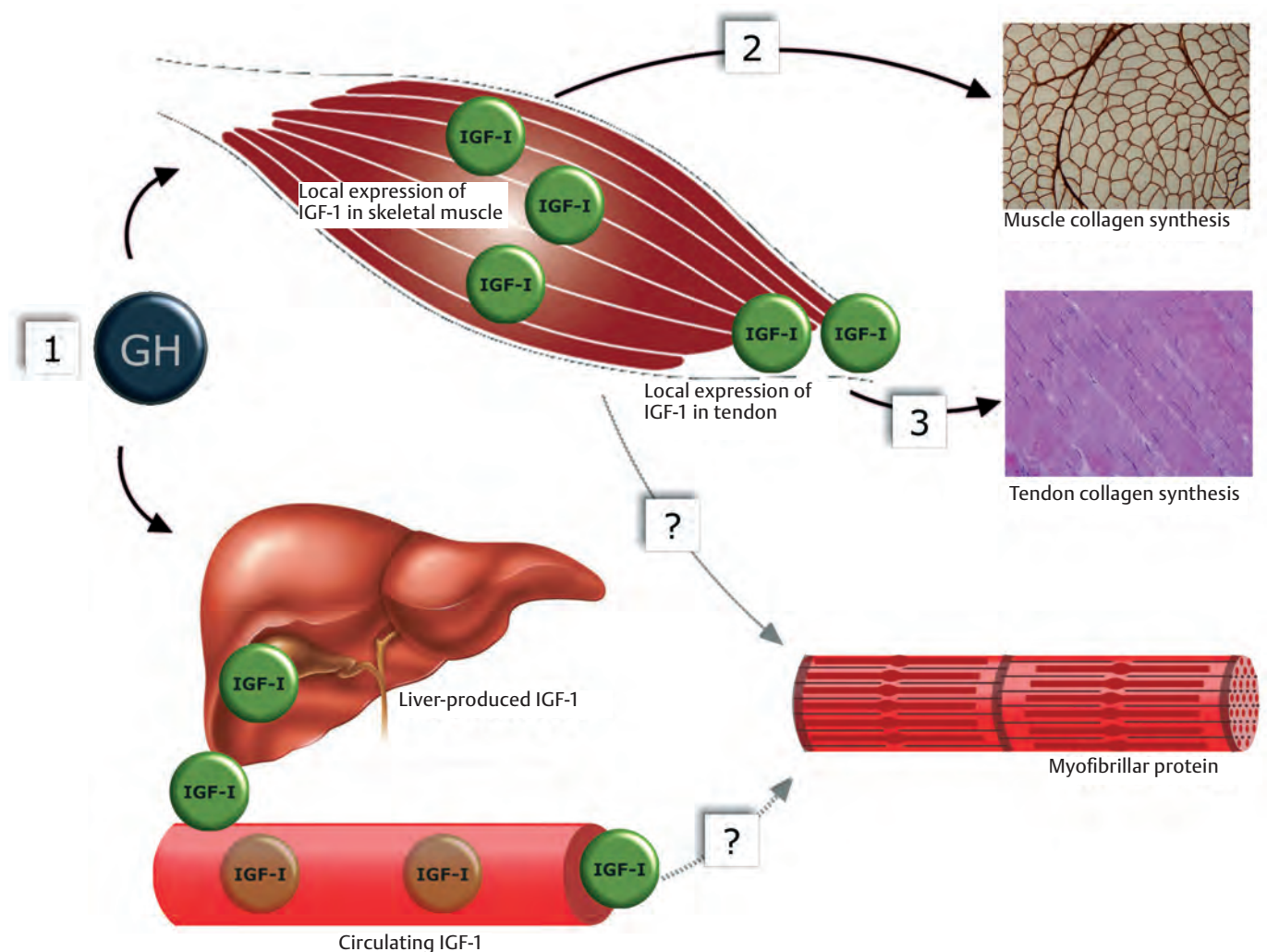


Figure 1. Effect of growth hormone (GH) supplementation on muscle and tendon tissue. (1) GH supplementation leads to increased circulating levels of IGF-I and to increased local expression of IGF-I in skeletal muscle and tendon. This is concurrent with increased expression of collagen in muscle (2) and tendon tissue (3). Myofibrillar protein synthesis appears unaffected by the increased levels of both circulating and local IGF-I levels (grey arrows).

potential to affect human collagen production. The specific association between the GH/IGF-I system and collagen synthesis is most evident in patients with acromegaly, where long-term elevated GH and IGF-I levels cause excessive growth of collagen tissues, including skin, bone and cartilage. In normo-endocrine

individuals GH supplementation is positively associated with collagen synthesis based on indirect whole-body measurements, and *in vitro* animal studies show that IGF-I increases tendon fibroblast collagen production. We recently observed that just 14 days of GH supplementation increased collagen

expression and collagen synthesis – up to 6-fold – in skeletal muscle and tendon in healthy human adults (Doessing *et al.* 2010). Moreover, in a recent (unpublished) study we observed a similar association between circulating GH/IGF-I and local musculo-tendinous collagen production in acromegalic and growth hormone-deficient (GHD) patients.

Growth hormone and skeletal muscle contractile/myofibrillar protein

The effect of GH on human muscle size/strength and contractile myofibrillar protein synthesis is a matter of controversy. While there is little doubt that GH/IGF-I increases muscle strength and contractive muscle protein synthesis in growing animals (Shavlakadze *et al.* 2010), a similar role for GH in skeletal muscle of adult normo-endocrine individuals is less evident. In our hands, there was no effect on contractile/myofibrillar protein synthesis of short-term GH supplementation in healthy human adults or of long-term alterations in GH titre in acromegalic and GHD patients. These observations are in concert with most previous human experiments where no effect on muscle strength and myofibrillar protein synthesis is observed.

Locally produced IGF-I as a potential paracrine/autocrine regulator of protein synthesis

The role of liver-derived circulating IGF-I as a primary peripheral mediator of GH actions is debated. Abolishment of hepatocyte IGF-I production has no effect on growth in mice, and it is suggested that systemic IGF-I primarily functions as a negative feedback regulator of pituitary GH synthesis. In contrast, locally produced IGF-I seems important in the regulation of local protein synthesis, including collagen. We observed that the expression of local IGF-I isoforms was up-regulated in GH-supplemented individuals (Doessing *et al.* 2010) as well as in acromegalic patients. Importantly, local IGF-I expression

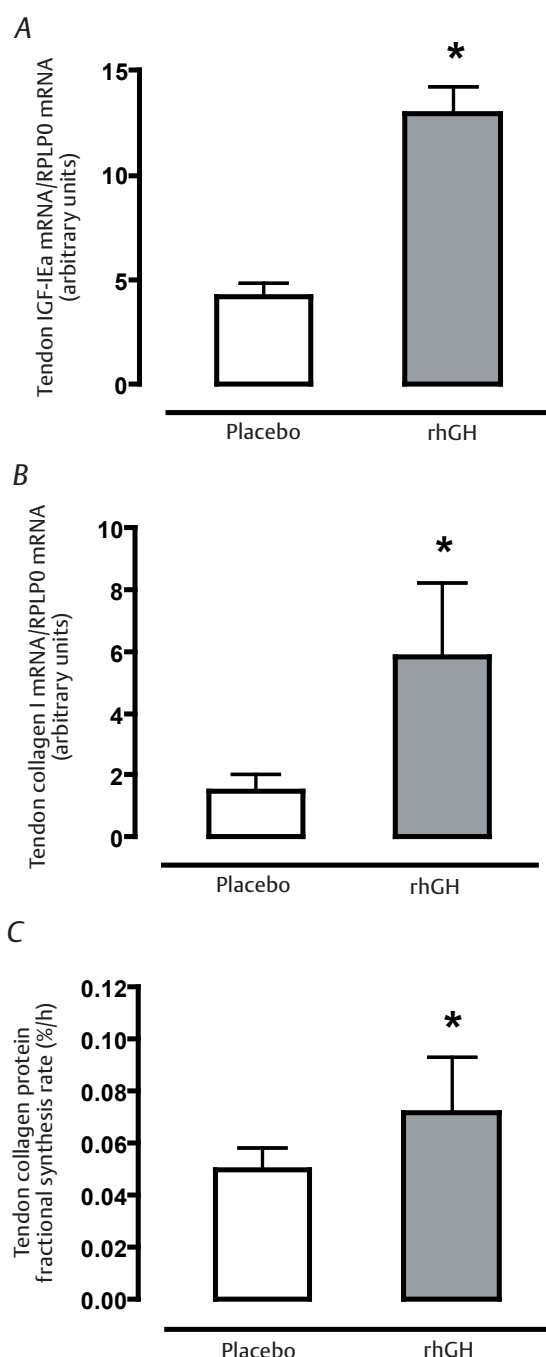


Figure 2. Tendon IGF-IEa mRNA expression, collagen I mRNA expression and collagen protein fractional synthesis rate. Young male participants ($n = 10$) were studied over 14 days in a crossover design with rhGH/placebo supplementation. mRNA data are geometric means \pm back-transformed S.E.M. A, IGF-IEa mRNA. B, collagen I mRNA. C, collagen protein fractional synthesis rate. *Difference between rhGH and placebo $P < 0.05$.

was closely associated with local collagen expression in both studies. This suggests that locally produced IGF-I could mediate the effect of GH on tissue protein synthesis in an autocrine/paracrine manner.

Doping with growth hormone

Doping with recombinant human (rh) GH and rhIGF-I is a widespread problem within a range of sports, from amateurs to professionals. GH and IGF-I are both on the World Anti-Doping Agency (WADA) list of banned substances and according to the 2007 Donati/WADA report it is estimated that more than 5 million people abuse rhGH worldwide. Anecdotal evidence suggests that GH is abused as doping by athletes partly due to its muscle anabolic properties. It is therefore a paradox that studies investigating the effect of GH supplementation on human adults show no effect of GH on muscle strength and contractile muscle protein synthesis. Interestingly, it is speculated by athletes, particularly within the bodybuilding community, that GH doping can prevent acute muscle and tendon injuries. Muscle and tendon ruptures are a common complication to heavy-weight training in combination with anabolic steroid abuse, and finding ways to strengthen the collagen connective tissue and thus decrease the risk of injury seems highly advantageous. As one bodybuilder described his GH experience: 'GH is probably the most remarkable drug at increasing collagen synthesis. It increases collagen synthesis in a dose dependant manner' (www.steroidology.com).

Interestingly, in a recent study on recreational athletes it has been shown that GH did not increase muscle mass but increased sprint performance when GH was administered alone or in combination with testosterone (Meinhardt *et al.* 2010). This finding is in accordance with the view that improved collagen formation after GH administration causes a more efficient force transmission in human skeletal muscle.

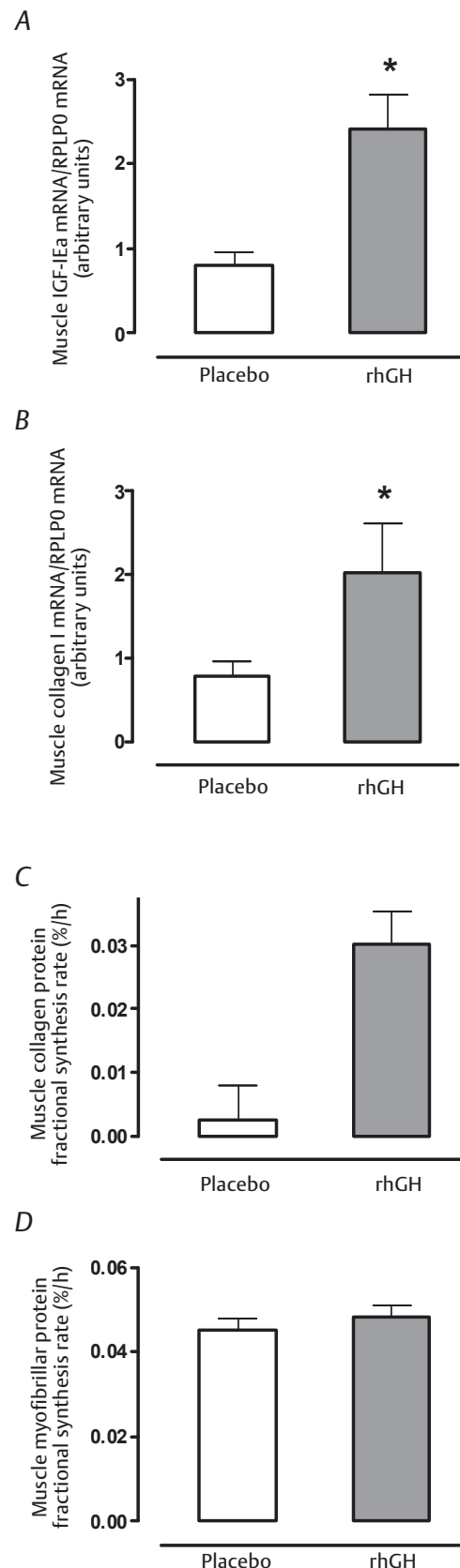


Figure 3. Muscle IGF-IEa mRNA expression, collagen I mRNA expression, collagen protein fractional synthesis rate and myofibrillar protein fractional synthesis rate. Young male participants ($n = 10$) were studied over 14 days in a crossover design with rhGH/placebo supplementation. mRNA data are geometric means \pm back-transformed S.E.M. A, IGF-IEa mRNA. B, collagen I mRNA. C, collagen protein fractional synthesis rate. D, myofibrillar protein fractional synthesis rate. *Difference between rhGH and placebo $P < 0.05$.

Does GH/IGF-I have a potential in the treatment of muscle and tendon injury?

The rumoured 'injury-preventing effect' of GH doping fits well with the observed effect of GH on collagen connective tissue observed in controlled experiments. It is therefore relevant to speculate whether GH has a potential in the treatment of over-use or acute muscle and tendon injuries. However, no studies have investigated the treatment potential of GH or IGF-I supplementation in relation to acute- or over-use muscle/tendon injuries in man.

Simon Doessing and Michael Kjaer

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Undergraduate Prize winners

Each year, The Society offers our Society Representatives the opportunity to nominate a student from their institution to receive an Undergraduate Prize for Physiology. Nominations can be for an outstanding student who has performed consistently well throughout their degree or for a student who has completed the best BSc Honours physiology research project.

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Congratulations to all students.

Generation of complex neuronal behaviour in a mammalian nervous system

Our understanding of motor patterns within mammalian neuronal networks has been limited by our ability to record activity in a large number of neurons simultaneously. We have used imaging techniques to explore a relatively simple mammalian neural network, the enteric nervous system, to determine how activity in different classes of neurons produces a complex motor behaviour.

The functional properties of a nervous system are largely determined by activity in individual neurons and the synaptic connections they receive or make on their targets. Networks of neurons that make synaptic connections with each other have emergent properties that aren't normally predictable by studying the characteristics of single neurons. Much of what is known regarding the function of neurons has been largely the result of studies of individual cells. Most studies have been restricted to invertebrates due to the relatively low number of neurons present, and their conserved neuronal topography, allowing for easy identification of the cells. Despite the small number of neurons, studies of invertebrate nervous systems have yielded insight into the functional basis of more complex motor events, such as swimming behaviour, rhythmic breathing and oscillatory activities such as chewing and locomotion. Similar studies on mammalian systems have been difficult due to the sheer number of neurons involved, their looser topography and the distance between neuron cell bodies and the targets they innervate. Studies in cortical slices cannot monitor physiological inputs or motor outputs.

The enteric nervous system (ENS) (Langley, 1900), or 'little brain', in mammals is one of the three subdivisions of the autonomic nervous system, innervating the alimentary canal, along with the gall bladder, pancreas and the bile duct. From a neuroscientist viewpoint, it is an intriguing system to study, as it is the only large collection of neurons outside of the CNS that is capable of generating its



From left to right:
Grant Hennig, Peter
Bayguinov and
Terence Smith

own reflexes and motor patterns. Neurons in the ENS are organized in a nearly two-dimensional manner in two well-defined plexuses, called the myenteric and submucous plexus. The myenteric plexus, which mainly regulates motility, is situated between the longitudinal and circular muscle layers, whereas the submucous plexus, which regulates secretion of water and electrolytes, lies in the submucosa close to the circular muscle. The complexity of the ENS can be appreciated by the fact that it contains approximately 10^8 neurons, roughly the same amount as in the spinal cord. Myenteric neurons in the large bowel form interconnected ganglia (roughly 1600 per cm^2), and each ganglion contains between 40 and 120 neurons, including sensory neurons, interneurons, and excitatory and inhibitory motoneurons with no obvious topography within each ganglia (Fig. 1A).

Slow and fast synaptic events in myenteric neurons can give rise to action potentials that generate robust and prolonged calcium transients that can be readily monitored using indicators such as Fluo-4. As Ca^{2+}

is ubiquitous in all excitable cells, determining the chemical coding of individual neurons requires *post hoc* labelling. In a recent study (Bayguinov *et al.* 2010), we used Ca^{2+} imaging in conjunction with immunohistochemical staining to report the activity of myenteric neurons simultaneously from several ganglia in the ENS, as well as the longitudinal and circular muscle, during the colonic migrating motor complex (CMMC) that would be impossible using traditional electrophysiological methods. The CMMC is a rhythmic, neurally mediated motor pattern in the colon which has been shown to underlie fecal pellet propulsion in mice (Heredia *et al.* 2009). To differentiate between the two major classes of motoneurons, we used NOS *post hoc* labelling to label inhibitory motoneurons.

In our recordings, we observed ongoing Ca^{2+} transient activity in many NOS⁺ (nitrergic) and NOS⁻ (cholinergic) Dogiel Type I myenteric unipolar neurons between the CMMC, yet there was little coordination of this activity among neurons in the same ganglion, or among neurons in different ganglia. NOS⁺ neurons often exhibited

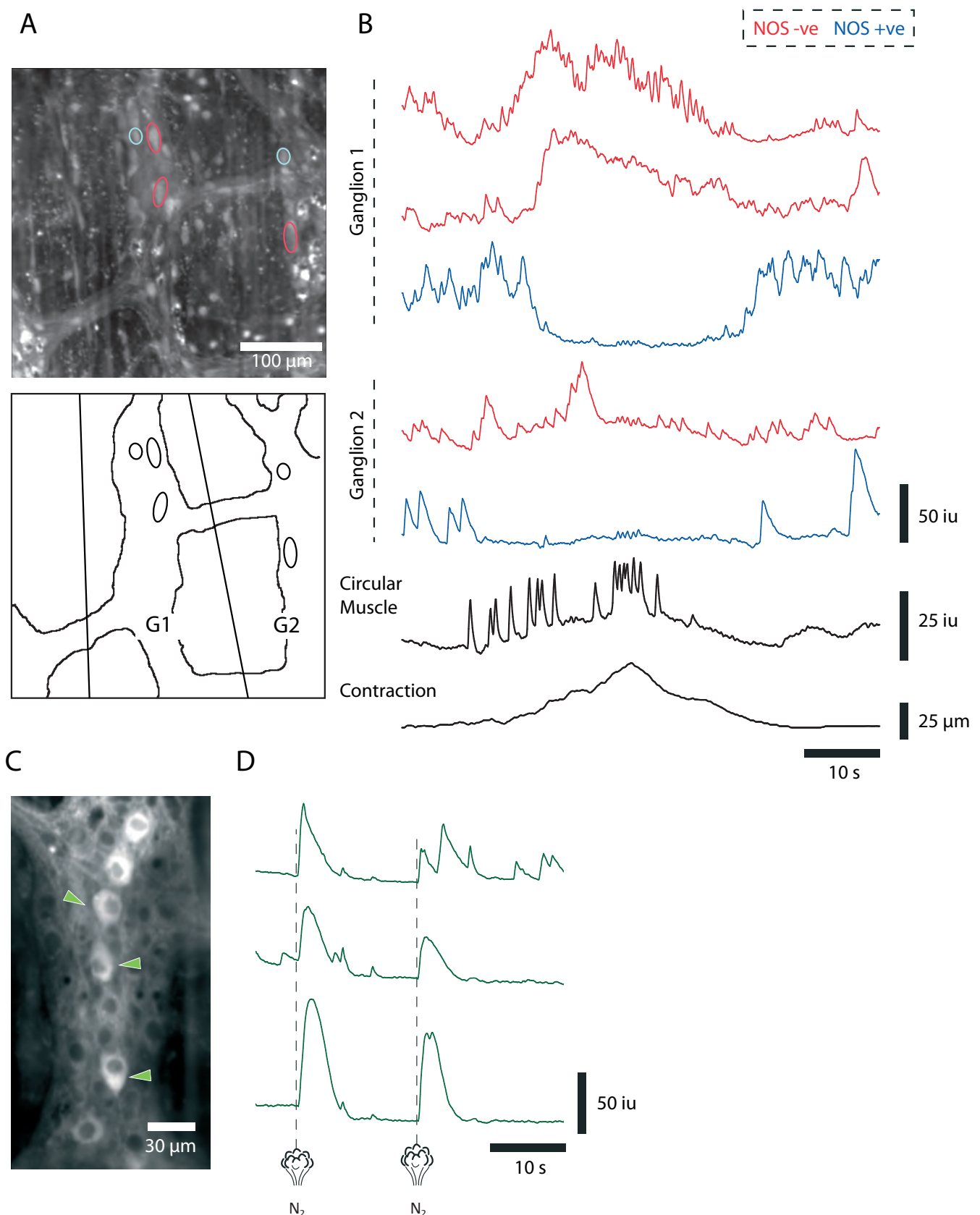


Figure 1. A, upper panel, two myenteric ganglia revealed by average Ca^{2+} fluorescence. Lower panel, silhouette showing outline of ganglia (G1 and G2). B, during the CMMC, NOS⁻ neurons (red) and NOS⁺ neurons (blue) increased and decreased their calcium activity, respectively. Ca^{2+} transients were measured in neurons situated in two different ganglia (see A, red and blue ovals). Note increase in Ca^{2+} action potentials in underlying circular muscle and associated contraction. C, myenteric neurons post stained with mitotracker. D, activity in 3 mitotracker⁺ neurons (see arrowheads in C) following two consecutive brief (45 ms) puffs of N_2 applied to the mucosa directly under the recording site.

rhythmic bursts of activity, that were probably responsible for mediating the tonic inhibitory input to the colonic muscle. At the onset of the CMMC, there was a synchronous activation of many NOS⁻ myenteric neurons (Fig. 1B, red traces), some of which remained active for the duration of the CMMC, suggesting that they were excitatory motoneurons that release ACh and tachykinins (TK) onto the muscle. This activation coincided with increases in Ca²⁺ transient activity in both the circular (Fig. 1B) and longitudinal muscle layers, leading to muscle contractions. Activity in a proportion of NOS⁺ neurons that exhibited rhythmic activity between CMMCs ceased just after the onset of the CMMC (Fig. 1B) and often remained quiescent even after the termination of the CMMC. This suggests that activation of excitatory motoneurons, together with a suppression of activity of NOS⁺ inhibitory motoneurons is necessary for the full and synchronous activation of both muscle layers during a CMMC.

Mechanical stimulation of the mucosa, applied at long distances away from the recording site (at

either end of the colon) evoked CMMCs, as visualized by a burst of Ca²⁺ transients in the muscle. Evoked CMMCs were not only similar in duration to spontaneous CMMCs, but also led to similar responses in the same myenteric neurons, with NOS⁺ neurons becoming quiescent, and NOS⁻ neurons increasing their activity. Moreover, mucosal stimulations at either end of the preparation evoked prolonged Ca²⁺ transient activity in multipolar Dogiel Type II neurons, which have projections to the mucosa, and are considered to be a major sensory neuron in the ENS. The fact that both oral and anal stimulation of the mucosa excited or inhibited the same myenteric neurons suggests that there is considerable convergence of interneuronal pathways onto common motoneurons.

We were interested in examining the responses of myenteric neurons at the site of stimulation, and, in particular, the activity of Dogiel Type II neurons, as these neurons were previously thought to initiate peristaltic reflexes but not the CMMC. Type II neurons were readily identifiable using mitotracker dyes

(Fig. 1C), since they, unlike other myenteric neurons, contain dense mitochondria. We found that Type II neurons appeared to be the first responders to local mechanical stimulation of the mucosa with a brush directly over the recording site, or a puff of N₂ applied directly to the mucosa under the recording site (Fig. 1D). Following several consecutive stimulations with a brush, there was a coordinated build-up of activity in these neurons, which led to the eventual initiation of a CMMC. Application of ondansetron (a 5-HT₃ receptor antagonist) greatly reduced these responses in Type II neurons, suggesting that they were being activated by 5-HT released from mechanosensitive enterochromaffin (EC) cells in the mucosa.

When the mucosa was removed from the colon, activity in myenteric neurons did not appear to be affected, as we observed similar ongoing Ca²⁺ transients in both NOS⁺ and NOS⁻ neurons, including Dogiel Type II neurons. Removal of the mucosa abolished the CMMC, and we failed to observe a single CMMC in 35 colonic preparations. Although the neural circuitry underlying the

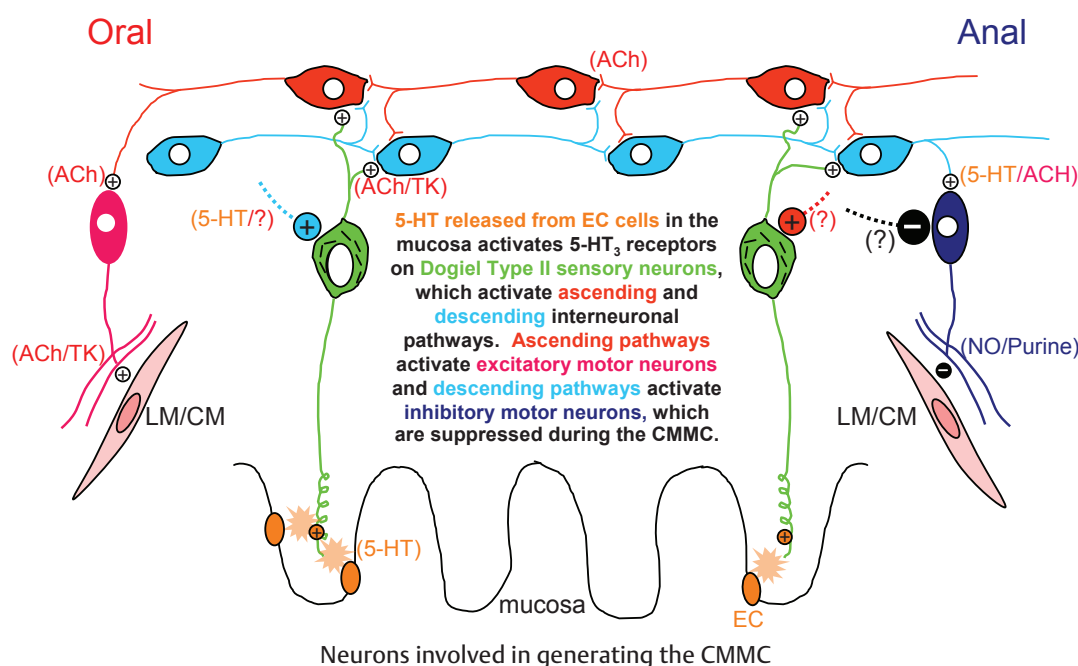


Figure 2. Idealized circuit underlying the CMMC. Note that following the initiation of the CMMC, activity in inhibitory (NOS⁺) motoneurons is suppressed.

CMMC appears to behave like a central pattern generator, as seen in invertebrates, input from the mucosa appears to be essential for bringing Type II neurons to threshold to initiate this motor pattern.

Unlike the peristaltic reflex (Bayliss & Starling, 1899), which is graded according to stimulus strength and conducts rapidly through the myenteric plexus, the CMMC appears to be an all-or-none event that propagates relatively slowly (0.8 mm s^{-1}) and probably requires the activation of Dogiel Type II neurons at different points along the colon for its regeneration (Fig. 2).

This study presents an important step in our understanding of how an integrated neural network in a mammalian nervous system functions to generate a complex rhythmic motor behaviour.

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Acknowledgements

This research was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (USA): RO1 DK45713. Calcium imaging was performed in a Core facility funded by NIH grant P20 RR-1875.

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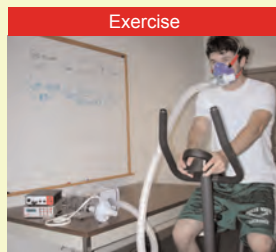
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'Sensible to feeling as to sight'¹

Some recent progress on mechanosensory transduction in mammals

Our understanding of the molecular basis of sensory excitation by mechanical stimulation in mammals remains rudimentary, despite its fundamental role in touch sensation, and blood pressure and movement control. But recent advances in the little roundworm, *Caenorhabditis elegans*, have provided clues that have led to evidence for a surprising candidate for a possible component of the transducer.

In 1993 Canessa, Horisberger and Rossier published a letter to *Nature* entitled 'Epithelial sodium channel related to proteins involved in neurodegeneration'. Although there is no hint of this in the title, the paper later proved to be a spur to research in one of the most intractable problems of mammalian sensory neuroscience: that of the mechanism by which neurons respond to touch, muscle stretch, blood pressure and similar mechanical stimuli. Canessa *et al.* (1993) had isolated and cloned a sequence from a rat colon cDNA library that hybridized with transcripts from various Na⁺-transporting epithelia. When they injected *Xenopus* oocytes with cRNA, the cells expressed an amiloride-sensitive Na⁺ current that was absent from controls. And when they searched databases for proteins with similar amino acid sequences to their newly discovered Na⁺ channel, which they called α rENaC, Canessa *et al.* came up with two members of the degenerin family of *Caenorhabditis elegans* proteins: *deg-1* and *mec-4*. The degenerins had been found by genetic screening for mutants of *C. elegans* that are insensitive to touch (Driscoll & Chalfie, 1992). They had been only partially cloned, so while their function was unknown, specific mutations of them caused certain mechanosensory neurons to degenerate during development. Canessa *et al.* (1993) proposed that the degenerins and ENaC belong to the same protein family (now generally called DEG/ENaC) consisting of ion channels involved in intra- and extracellular volume control, and that might also include mechanosensitive ion channels.



Guy Bewick and Bob Banks (left to right).

The DEG/ENaC family continued to enlarge with the addition of the molluscan FMRFamide receptor, Ripped Pocket (RPK) and Pickpocket (PPK) from *Drosophila melanogaster* and the mammalian acid-sensing ion channels (ASICs, also known as brain sodium channels, BNC or BNaC), as well as further ENaC subunits. All are characterised as contributing to non-voltage-dependent, amiloride-sensitive ion channels selective for Na⁺ (Kellenberger & Schild, 2002). Meanwhile the cross-fertilization engendered by the original union of the degenerins and ENaCs in one family was beginning to produce mechanosensory fruit. To date this has developed best on the nematode

branch of the phylogenetic tree, where early indications that *mec-4* and the related *mec-10* might constitute a Na⁺ channel as part of a multi-protein complex responsible for detecting light touch have been borne out (O'Hagan *et al.* 2005). Reciprocally, the recognition of the likely involvement of degenerins in nematode mechanotransduction soon led to suggestions that the ENaCs, and later the acid-sensing ion channels (ASICs), might be similarly important in mammals.

In the first such study, Drummond *et al.* (1998) used RT-PCR to demonstrate that β - and γ -ENaCs are expressed in the nodose ganglion of rat, which contains neurons that supply baroreceptor endings to the aortic arch. Although the pore-forming α -subunit was not found by them, Drummond *et al.* did find that amiloride inhibited the response of the ganglion cells to mechanical stimulation (assessed as a rise in intracellular [Ca²⁺]), and that benzamil, an amiloride analogue, reduced both the response of

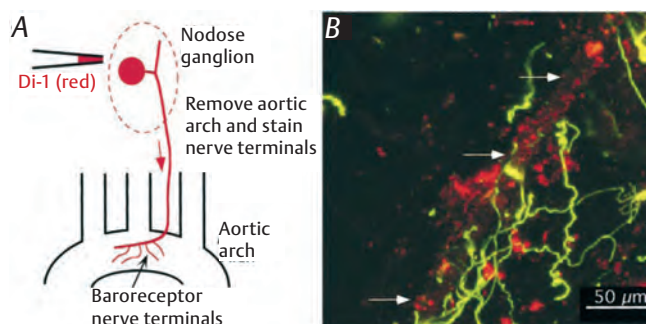


Figure 1. Immunofluorescence localization of γ ENaC in rat aortic arch baroreceptor nerve terminals. **A**, labelling baroreceptor nerve terminals in aortic arch. Di-I injected into the left nodose ganglion diffused anterogradely to the baroreceptor terminals. **B**, two weeks later the aortic arch was removed, immunolabelled for γ ENaC and examined by fluorescence confocal microscopy. Di-I is red, γ ENaC is green, while nerves labelling with both are yellow. A large Di-I-labelled axon/small nerve bundle (arrows) descends diagonally from the upper right to the lower left. Smaller side branches from this appear yellow, indicating that γ ENaC is expressed in the Di-I-positive baroreceptor terminals of nodose ganglion neurones. (Adapted from Drummond *et al.* 1998, with permission from Elsevier.)

¹Macbeth Act 2, scene 1.

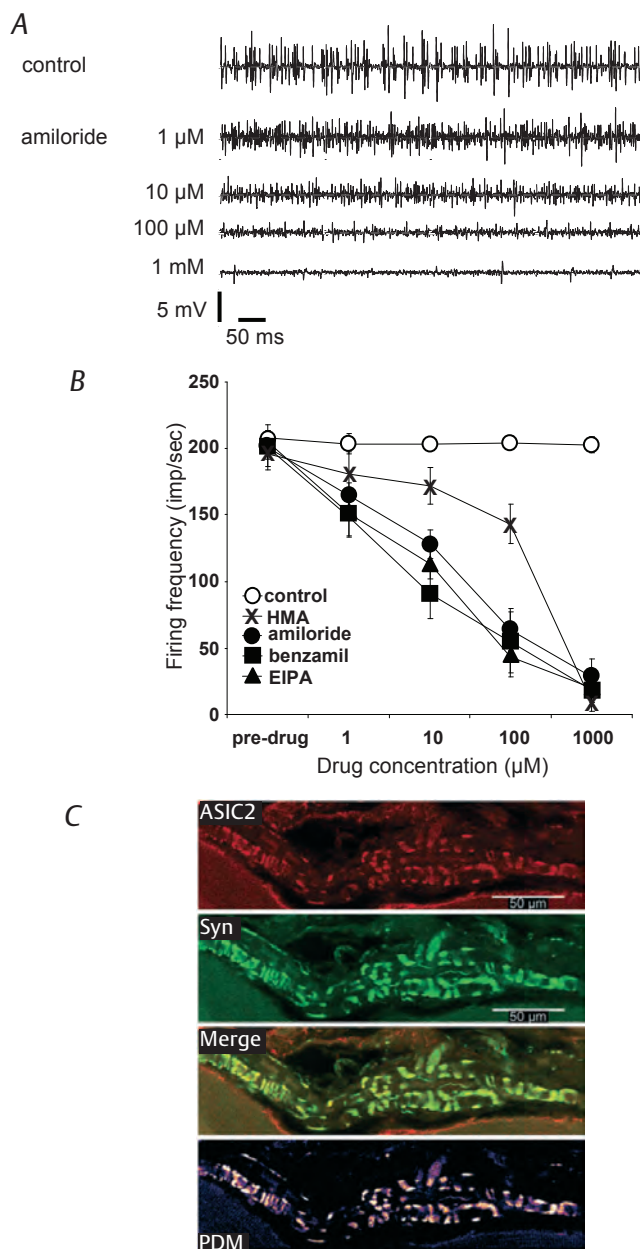


Figure 2. A, stretch-evoked spindle afferent discharge is sensitive to the ENaC blocker amiloride and analogues. Electroneurograms of static-phase spindle spiking during 1 mm stretches of rat 4th lumbrical muscles. Increasing amiloride concentrations reduced spiking frequency. B, comparison of inhibition of afferent discharge by amiloride and its analogues. Amiloride, benzamil and EIPA produced equipotent inhibition of firing; HMA had little effect below 100 μ M, but produced almost total abolition at 1 mM. C, intensity correlation analysis shows ASIC2 colocalisation with synaptophysin. Representative images of a spindle primary ending double labelled for anti-ASIC2 (red) and anti-synaptophysin (green) immunofluorescence to demonstrate intensity correlation analysis after the method of Li *et al.* 2004 using ImageJ software. The third panel is the merge of the first two with colocalisation appearing as yellow/orange. The fourth panel is a new image where each pixel is equal to the product of the differences from the mean (PDM) for each pixel, calculated as follows:

$$(\text{red intensity} - \text{mean red intensity}) \times (\text{green intensity} - \text{mean green intensity}).$$

The image is pseudocoloured according to PDM (blue, modest colocalisation; red, higher; white, highest); pixels that are below average in both channels are excluded (black). Colocalisation is especially high within the sensory terminals, as shown by white pixels. ASIC2 immunoreactivity is clearly colocalised with that of synaptophysin in the sensory terminals. Immunolabelling for each of the four ENaC subunits colocalised with synaptophysin staining in a similar manner. (Adapted from Simon *et al.* 2010.)

rabbit carotid sinus baroreceptors to blood pressure and the resulting pressor reflex. In addition, they used immunocytochemistry to localise γ -ENaC to the sensory endings and ganglion cells (Fig. 1). A similar study, also by Drummond *et al.* (2000), on rat cervical and lumbar dorsal root ganglion cells came to similar conclusions, but in this case the techniques were confined to RT-PCR and immunocytochemistry. Antibodies against both β - and γ -ENaCs were used to localise the proteins to the sensory endings of Merkel-cell afferents (though not the Merkel cells themselves), Meissner and lamellated corpuscles of the foot pad. At the same time, and using the same techniques, Fricke *et al.* (2000) reported the presence of α -, β - and γ -ENaCs, and stomatin in rat trigeminal ganglion cells and the lanceolate terminals of vibrissa sinus hair follicles, innervated by the trigeminal ganglion. Stomatin is homologous to *mec-2*, which is thought to be important in linking the *mec-4/mec-10* ion channel to the cytoskeleton in *C. elegans*.

The ASICs are another branch of the DEG/ENaC family, distinct from both the degenerins and the ENaCs. Price *et al.* (2000) generated a mouse with a BNC1 (ASIC2) null mutation by homologous recombination to disrupt the gene. Then, using an *in vitro* skin/nerve preparation, they found that both rapidly and slowly adapting mechanoreceptors showed reduced responses to defined stimuli. In other respects, the phenotypes of the homozygous mutant mice appeared quite normal. By immunocytochemistry, Price *et al.* localised BNC1 (ASIC2) to hair follicle sensory endings, particularly the lanceolate terminals of palisade endings; shortly afterwards, Garcia-Añoveros *et al.* (2001) demonstrated that the splice variant BNC1 α is targeted to the peripheral, but not the central, projections of dorsal-root ganglion cells where it was localised in the sensory terminals of several types of mechanoreceptor in glabrous and hairy skin.

For ten or so years now, we have been working on transduction in the

muscle spindle, that most complex of mammalian mechanosensory receptors (after the ear). The muscle spindle has a special place in sensory and synaptic physiology due, primarily no doubt, to its innervation by the largest afferent axons in the body and their monosynaptic connexions with motoneurons in the neuraxis, but also to the relative ease and precision with which stimulation by muscle stretch may be delivered to it. The sensory terminals of muscle spindles are, of course, the peripheral endings of dorsal-root ganglion (DRG) cells and so might be expected to share some functional properties with other mechanosensory DRG cells. The recent paper from our group in *The Journal of Physiology* (Simon *et al.* 2010) lends support to this hypothetical similarity of function. There we show that amiloride and several of its analogues can greatly inhibit, or even completely block, the sensory response of the muscle spindle to a maintained stretch, and that this is unlikely to be due to effects on action potential transmission (Fig. 2). We also present biochemical evidence for the expression of at least three of the ENaC subunits – α , β and γ – in muscle spindles and immunocytochemical evidence for the localisation of ASIC2 and the ENaC subunits in the sensory terminals.

This much, then, is consistent with the earlier studies implicating members of the DEG/ENaC family in mechanotransduction by touch- and baroreceptors. But we also showed that ASIC2 and the ENaCs are colocalised with synaptophysin in the spindle's sensory terminals, so linking the possible primary events of mechanotransduction with the system of 'synaptic-like vesicles' (SLVs), previously described by us (Bewick *et al.* 2005). SLVs are certainly not unique to muscle spindles (Fig. 3), and may be a common feature of mechanosensory endings, at least those of primary afferent neurons. In our use of the spindle as a model for this system

we (Bewick *et al.* 2005) showed that the SLVs appear to be part of a glutamatergic mechanism for the auto-regulation or modulation of the sensory terminals' excitability. The SLVs recycle to and from the terminal membrane in an activity-dependent manner, both exo- and endocytosis being Ca^{2+} dependent, and probably release glutamate which acts via a non-canonical phospholipase-D-linked metabotropic glutamate receptor

(mGluR) to maintain, or increase, the excitability of the terminals themselves (Fig. 4). The mechanism is of fundamental importance to mechanotransduction, since specific antagonism of the mGluR by the glycine derivative PCCG-13 can reversibly silence the output of the sensory ending, possibly as a result of receptor-mediated inactivation of the primary mechanotransducer (a protein complex possibly including ASIC2/ENaC) at the terminal

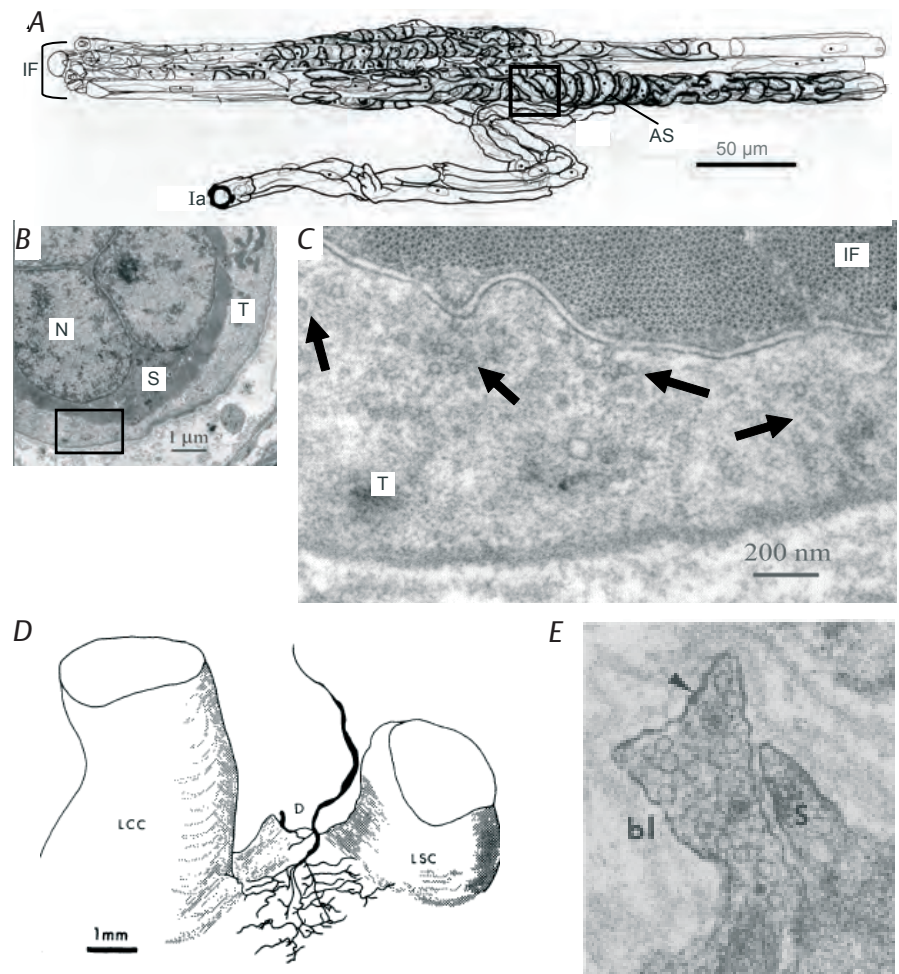


Figure 3. Synaptic-like vesicles in mechanosensory endings. *A*, cat primary annulospiral (AS) sensory endings enclosing intrafusal muscle fibres (IF) reconstructed from serial transverse sections. The myelinated Ia afferent sensory axon (Ia) enters from below before branching to encircle the fibres. *B*, transverse section through an intrafusal bag fibre, as for the boxed area in *A*, showing the accumulation of nuclei (N) in the sarcoplasm (S) and how it is enclosed by the annulospiral terminal (T). *C*, clusters of 50 nm, clear 'synaptic-like vesicles' (SLVs - arrows) in a Ia afferent terminal (T). Note that SLVs cluster on both aspects of the terminal, both adjacent to and away from the intrafusal fibre (IF). *D*, drawing of a methylene blue-stained rat aortic nerve whole mount, as seen through the dissecting microscope. Part of the dorsal branch (D) is visible, along with the ventral branch. LCC, left common carotid artery; LSC, left subclavian artery. Drawing by Gary Matsuoka and Jo Long. *E*, a process of an unmyelinated axon terminal containing many SLVs and two dense-core vesicles. Note that the Schwann sheath (S) does not cover the process completely but the basal lamina (bl) does. Arrowhead, membrane 'thickening'. $\times 60,000$. (*D* and *E* adapted from Krauhs, 1979, with kind permission of Springer Science and Business Media).

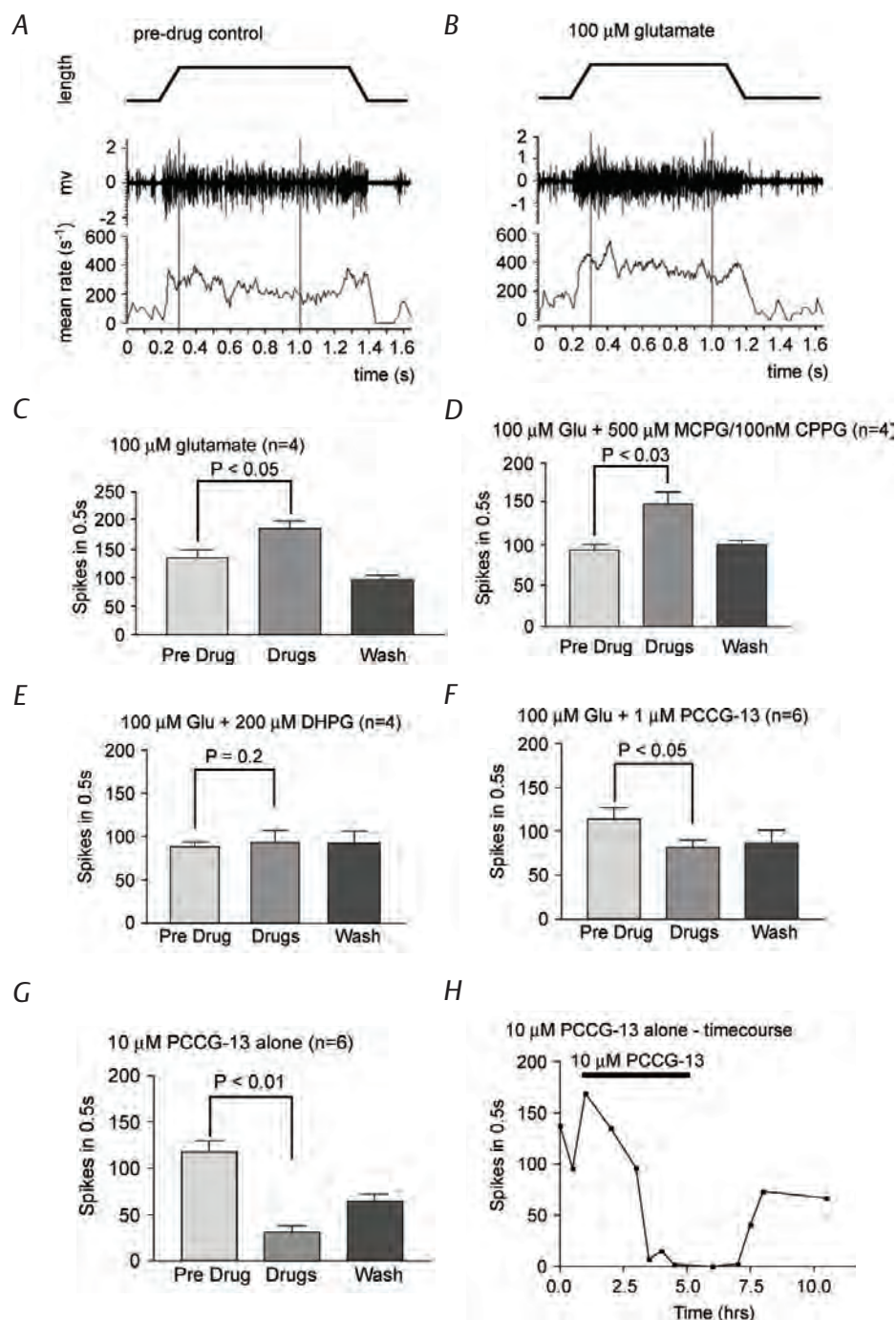


Figure 4. A and B, glutamate increases afferent discharge frequency during stretch-and-hold cycles. Rat 4th lumbrical muscle spindle increases in the absence (A) and presence (B) of exogenous 100 μ M glutamate. Electroneurogram (middle plot) and mean firing rate (lower plot) of total afferent discharge from the whole nerve during a 1 mm stretch-and-hold cycle (upper plot) are shown before and ~150 min after glutamate application. C–H, only antagonists of PLD-coupled metabotropic Glu receptors (mGluRs) block this glutamate-mediated increase in spindle excitability. C, mean data (4 preparations, \pm S.E.M.) showing a significant and reversible increase in afferent discharge to glutamate. D, the enhancement is not mediated by group I–III mGluRs, since broad-spectrum receptor antagonists MCPG (group I/II) and CPPG (group II/III) do not inhibit this effect. Kynurenate (1 mM; data not shown), a broad-spectrum ionotropic GluR antagonist was also ineffectual. E, (R,S) 3,5-DHPG (200 μ M) blocked the glutamate-mediated excitability. DHPG is a type I mGluR agonist but is also an inhibitor of a non-canonical phospholipase D-coupled mGluR. F, PCCG-13, a selective PLD-mGluR antagonist, also abolished the effects of exogenous glutamate. G, evidence for the importance of endogenous glutamate release came through application of PCCG-13 alone. PCCG-13 markedly reduced spindle discharge frequency in the absence of exogenous glutamate, but required higher concentrations (10 μ M). This is consistent with PCCG-13 blocking receptor activation by tonic release of endogenous glutamate. H, a representative experiment showing the time-course and profound effect of PCCG-13 applied alone on the responsiveness of a spindle to stretch. Stretch-evoked responses were well maintained in the absence of drugs (time-matched controls, not shown). Statistical probabilities: Student's paired *t* test, pre-drug versus drug. (Adapted from Bewick *et al.* 2005.)

membrane, or its sequestration within the terminal in the membranes of the SLVs.

Perhaps the main reason the molecular basis of mechanosensation has been so elusive in all its forms in animals, and especially mammals, is its unlooked-for complexity. What we have briefly described here may well prove to be an important part of the story, but it will certainly not be the whole story. Thus, whereas DEG/ENaCs may constitute an important ion channel, other ion channels from other protein families (transient receptor potential, or TRP, channels perhaps) are also likely to be important in at least some sensory endings. And, even if the principal ion channels and some aspects of their functional expression have been identified, their gating mechanism remains essentially unknown. Exciting times, indeed!

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<http://jp.physoc.org/content/588/1/171.full>

Intermittent hypoxia: from molecular mechanisms to clinical applications

Edited by Lei Xi and Tatiane V Serebrovskaya, Nova Science Publishers Inc. 2010, pp. 615, £75 ISBN 978-1608761272

This book describes in 30 chapters, with contributions from 75 authors from 17 countries, the subject of intermittent hypoxia. In the foreword the authors state that the aim of the book is to enlighten Western scientists on a topic that, although considerable research has been carried out on the subject, is not as visible as it should be due to the majority of the research being carried out in the former Soviet Union during the Cold War. The chapters are arranged in six sections describing aspects of intermittent hypoxia in relation to: (1) the cardiovascular system, (2) the respiratory system, (3) the nervous system, (4) genetics and molecular biology, (5) sports training, and (6) clinical and therapeutic strategies.

It is well known that the higher one ascends, the 'thinner' the air becomes, such that above 3500 metres the decrease in partial pressure of oxygen can impair normal physiological processes. An extreme example is the death zone referred to by mountaineers climbing Mt Everest where above 8000 metres there is so little oxygen present the body cannot acclimatize. What the book attempts to do is to describe how such low oxygen content negatively affects the body, but also how it can be harnessed to improve performance or be used as a clinical strategy.

One negative aspect of the book is the poor English in some of the chapters. This is confronted in the introduction where the editors state 'we have attempted to assist these groups of researchers to overcome their language barriers.' However, the opening sentences of the first chapter: 'The science is always inverted to the future. At the same time it is connected with the past closest among all ranges of human activity.' suggests

a hard slog awaits the reader. While on the subject of the book's deficiencies, the quality of some of the illustrations (all black and white) leaves a lot to be desired, clear pixilation visible on many of the images. The format of the book, i.e. chapters written by individuals, leads to a mix of styles, with some written as reviews, and others in the style of scientific papers with results, methods and discussion sections.

Overall I felt there was an imbalance towards the effects of intermittent hypoxia on the cardiovascular or respiratory system (14 chapters) with only three on the effects on the nervous system. In addition, I felt the clinical implications were underrepresented (3 chapters). However, such caveats should not deter the interested researcher from this book. It is the most complete book on the topic so far, and if one can get beyond its superficial deficiencies there is a multitude of data on offer, that is unavailable elsewhere.

Angus Brown

Sense About Science Media Workshop

Over the last few years, I'm sure I'm not alone in observing a generalised shift in the thinking of the scientific community. The words 'translational research', 'bench to bedside' and 'communication' are forever ringing in my ears. Every day, emails drop into my account looking for volunteers to talk in schools or at public events. It is this shift that has recently got me thinking about the world of science and health communication, and how we can work to make science relevant and understandable to everyone. For that reason, when I saw an advert for the aptly named 'Standing up for Science Media Workshop', it seemed the perfect opportunity for me to understand more about how scientific data come out of the lab and on to the front pages.

The workshop, run by Sense About Science, a small charity that aims to equip people with the tools to make sense of science, was a chance to see things from all sides of the story. Our first session involved three scientists who had varying degrees of exposure to the media. They gave us hints and tips on the good, the bad and the ugly of presenting data to the press. I'll admit I was surprised to find that their experiences were generally good, although some reservations and apprehension still existed and caution was urged. What was most prominent to me from what they said, was the need to keep things simple and have as few points as possible to avoid any twisting or misunderstanding of data. They were all great in actively encouraging us to engage with the media and portrayed it as an exciting and necessary part of our jobs. One of the issues raised in this session really got me thinking. It drew attention to the issues surrounding the current UK libel laws and the effect these have on the ability of the scientific community to debate freely in print. Through this we learned of the important work of Sense About Science on libel reform and I have since signed their petition to change the laws (www.libelreform.org).

The second session was from the opposite angle and this time three journalists took the hot seat. If I'm honest, at the beginning very few people had positive things to say; however, once the debate opened up and discussion was flowing freely, several things quickly became clear. All three panellists had an evident passion for their jobs and, more importantly, they were all sincere in their desire to report accurate science. They were also keen to impart on us our responsibility in the process and the key things that we should remember; scientists need to be as open and informative as possible and remember that competition for column inches is rife, and that the best way to make a story saleable is to make the science relevant to people's lives. I think, for me, what this session did, was open my eyes to what journalists need and dispel some of the myths surrounding miscommunication and scaremongering. After all, they are there to sell newspapers, but it's in no one's interests to sell the wrong story.



The final session pushed home the need for young scientists to get involved in science communication and myth busting and also gave us advice on how to get our own work 'out there'. Along with useful hints and tips from a university press officer, we also learned about the Voice of Young Science Program (VoYS). I was incredibly surprised and impressed to hear that the VoYS initiative had recently been involved in the headlines surrounding the futility of the January 'detox' as well as speaking out against homeopathy being used as 'effective' treatments for life-threatening illnesses in the developing world. The latter campaign even managed to get the

WHO onside. This highlighted to me that with enough knowledge and a lot of determination, we can all make an impact on science communication. I think this is hugely inspiring and encouraging to any scientist and I look forward to learning more about and engaging with, the VoYS community.

All in all, the day was hugely rewarding and I came away feeling strongly that a synergistic and lively communication between scientists and the media is imperative on numerous levels. The more effectively and excitingly we portray our data, the more we are giving the journalists what they need to do their job successfully. This lessens the likelihood of misreporting or preposterous headlines. In an age where the public's demand for scientific knowledge is growing and where access to technical information is only a click away, surely the only way to ensure that precise and effective messages are communicated is to exploit the symbiosis of the relationship between science and the media, and use that to our mutual advantage to prevent miscommunication whilst still conveying science to large audiences.

Members of The Physiological Society have priority places on these workshops and the next one will be in Edinburgh on 16th November. For further information about Voice of Young Science (VoYS) and future workshops please visit the website (www.senseaboutscience.org/VoYS) or contact Julia Wilson at jwilson@senseaboutscience.org

Laura McCallum
King's College London

Physiology News

If you have enjoyed this issue of *Physiology News* please don't throw it away. Put it in your coffee room so that others may see it too.

We are always looking for interesting features, meeting reports, news items and photographs. Contact us at magazine@physoc.org with your suggestions.

Biology and education

Everybody is an education expert – at least that's what many people think: after all we are all 'customers' of education systems and processes at some point in our lives. The reality, however, is that education policy and practice is enormously diverse and equally complex, ranging from engaging young primary school children through to vocational and academic qualifications. There are a multitude of acronyms and a confusing array of institutions involved.

The Society of Biology is an active participant in education issues. As well as influencing policy, we also have a key role in helping with interpretation of the jargon that so often surrounds education debates. With that in mind, the Society will be holding a seminar this autumn to help any of our members who are not experts, get under the skin of education policy and how exams are set and assessed, perhaps helping to answer the hotly debated issue as to whether exams really are getting easier.

It is a good time to create momentum around education. Michael Gove, our Minister for Education has already indicated a likely shift to more 'traditional' A Levels, with the abolition of AS exams along the way. The exam regulator OFQUAL has rejected the examining boards' proposals for new specifications for the GCSE examinations and the Qualifications and Curriculum Development Authority (QCDA) is to be abolished. These are significant changes that need to be monitored and influenced.

During the course of this year, the Society has been working with our Member Organisations to create a strong voice for biology, working both independently and with the other sciences, especially through SCORE (Science Community Representing Education). There has been real progress with the proposed new specifications for biology progressing much further than some of the other disciplines. In the past, some have positioned biology as the easy option, especially amongst the sciences. But the evidence shows exactly the opposite. According to a range of



independent measures, biology scores as one of the hardest A levels. In terms of relative grading, it is two grades 'harder' than some other disciplines. But we need to be careful to ensure biology stays relevant and focused on skills, not just knowledge. Practical training has always been under threat. It is more complicated in biology than many of the other sciences and certainly at university level, becomes extremely expensive. As the new coalition Government starts to review spending cuts across the public sector, the Society will be campaigning hard to ensure biology doesn't lose out. It would be all too easy for Government and the university sector to move away from hands-on practical skills in the laboratory and in the field in favour of the cheaper option of demonstrations or videos. For that reason, practical skills will continue to be a focus of our work at all levels. The Practical Biology website has proved increasingly valuable to biology teachers and we now need to ensure it grows and becomes sustainable.

As well as influencing formal education policy all learned societies must help show that the sciences are exciting as well as contributing significantly to our society and the economy. How often have we heard that it was an inspirational teacher that attracted someone into the study of biology? In a world of limited resources, we must make sure that teachers continue to be strongly supported with continual professional development available and resources easily accessible to help them make the current curriculum as engaging as possible, providing opportunities for study outside of core material to enrich learning. The Society of Biology will be pushing this independently, and through SCORE, and working closely with other institutions such as the National Science Learning Centre to ensure material is as widely available as possible.

Having succeeded in engaging students in studying biology, there is a further challenge of ensuring they maintain their association with the subject. To do

that we need interesting and relevant careers material to help make choices. With this in mind, the Society is pulling together new resources for careers but will aim not to reinvent the wheel. Our Member Organisations have a wealth of material which needs to be drawn together and made available to all biologists, not just those in particular disciplines.

Mark Downs

Chief Executive
Society of Biology

Question to the Membership: future spending proposals

At the AGM 2010 in Manchester, I outlined the current financial position of The Society and indicated that the Trustees wished to increase charitable expenditure. Areas identified by the Trustees for new or increased activity include:

- **Pump Priming Grants**
Competitive wards of ~£15,000 to Members in academic institutions.
- **Outreach to schools**
- **Public engagement**
- **Meetings**
Proposals to increase the number of themed meetings.
- **Summer Student bursaries**
Increased availability

Further information will be posted as the details of the activities are formulated, including application guidelines for competitive awards.

The Trustees would welcome any comments by Members on the above proposals, as well as any further ideas for increasing charitable expenditure. Due to the unpredictability of future publishing income, proposed activities should be capable of relatively rapid expansion or contraction, and ideally avoid long-term major financial commitments.

Comments and suggestions please to cearly@physoc.org

Rod Dimaline

Honorary Treasurer

A call to cleanse the genome of semantic silliness

One distinguishing feature of modern genomics is not its capacity to illuminate but a serious inclination to flirt with silliness. In particular, one form of silliness has caused me serious confusion and has even upset my head of department.

It is the use of silly and functionally inconsistent gene names.

Who let a range of the pathologically narcissistic, the morally deficient, the champions of pseudo-intellectual genomic obscurantism and orientalism and the plain clinically weird loose on the genome? Clarity and scientific rigour to these people are what usury was to the medieval church. What use is systematically naming large numbers of the 22,000 genes of the genome in a way that is inconsistent across species, does not relate to function and acts merely to plant a disturbed image in the brain.

I would like to logically deconstruct – perhaps rant about would be more accurate – two categories of semantic genomic silliness.

Genes with multiple identities or aliases

Take the immediate early response gene NGF1- α , it has too many names and none of them are fit for purpose. For those of us who like the letter z in our rat genes, it can be called ZIF-268. Then it gets complicated. In mice it is called early growth response gene 1 (EGR-1) and a man called Bernard once called it transcription factor ETR103. I once spent many hours on the NCBI database trying to locate an avian gene sequence for NGF1- α . Not one bird NGF1- α , ZIF-268, EGR-1 or ETR103 gene sequence exists. That's because some comedian has named the avian form ZENK.

Genes with a silly name

If you are the type of person who thinks train spotting is an erotic pastime, you could, for a bit of light relief, go for an extended trawl

through one of the genomic databases (Ensembl or NCBI for starters). Embedded in lists of boring genes concerned with totally useless things like signal transduction and histone regulation there are hundreds of genes with really interesting names. There are genes in this subgroup that are able to irritate and distract any scientist. The names draw you in like a moth to a candle.

The problem is that I can never work out what they actually do.

I recently came across five gene names that I thought would appeal to a range of disturbed scientific minds. They are presented here with their inferred physiological function that I derived from several hours of studying their names. They are also prefixed so that physiologists with varying degrees of psychological dysfunction can find them interesting and accessible.

1. For the religiously minded – *Angel in Drosophila*

When expression of this gene is increased a fly is bathed in a white light, and a supernatural fly with gossamer wings hovers in the air soon after. *Angel* is an immediate early onset gene that transiently appears in times of great distress, such as when a fruit fly is menaced by a spider.

2. For the orientalist – *Sumo in Drosophila*

Two flies gain enormous amounts of weight, wrap a ceremonial cloth around their legs (which is no mean feat when you have six), throw salt over their shoulders and engage in prolonged wrestling bouts. Analysis of this gene should give profound insights into the cause of obesity in East Asian communities.

3. For the criminal psychologist – *Headcase in Drosophila*

A fly barricades itself in a plastic flask, takes several other flies hostage and refuses to leave unless its demands are met. A gene useful



for the study of interpersonal interactions in socially deprived inner city areas. Or in universities.

4. For those of an artistic temperament – *Van Gogh in Drosophila*

A fly paints vibrant post impressionist pictures on the walls of its plastic flask, before removing its right antenna which it posts to an ex-girl friend. The fly dies tragically soon afterwards and the decorated flask is then sold for \$20 million at Sotheby's. Analysis of this gene could provide useful insights into the processing of visual information in the cortex of the clinically insane.

5. For the clinically sexually weird – *Menage a Trois in vertebrates*

In the early 1970s Paris, a middle-aged male mouse with commitment issues, meets two free-spirited but younger female mice and manages to entice both of them back to his nest. This induces dramatic increases in expression of the gene sequence '*Menage a Trois*' which turns a sexually fading mouse into a rampaging sexual athlete. However, any further discussion of this gene is subject to a confidentiality agreement with the drug company Pfizer. Note that the patent on Viagra runs out soon.

One gene name I did like and that was very functionally descriptive was '*Defender of cell death*'. I visualise this gene as a protector, a vigilante – sort of a post modernist genomic version of Charles Bronson from the film '*Death Wish*'.

Dr Keith Cormorant has a range of unusual single nucleotide polymorphisms in his '*Menage a Trois*' gene.

The influence of oxygen inhalations on muscular work

Leonard Hill & Martin Flack (1910)

J Physiol **40**, 347–372

In my looks back at *The Journal* of a century ago I am struck by the consistency with which the papers report experiments that have become staples of practical class physiology, doubtless familiar to many readers. One such experiment is asphyxia, typically via rebreathing from a spirometer, or breath-holding. As is intuitively obvious, a 'limit' occurs when the subject cannot continue, often called the break point. A century ago physiologists were rationalizing these phenomena, and the control of respiration in general, in terms of the partial pressures of O₂ and CO₂ in alveolar air. One such physiologist was Leonard Erskine Hill (1866–1952).

The 1910 paper is the second part of a pair, the first part being a paper by the same authors two years previously:

"In our last paper in this Journal (Vol. 37, 1908, p. 77) we brought forward evidence which showed that the duration of the period in which the breath can be held depends on the relative partial pressures in the alveolar air of O₂ and CO₂... Under ordinary conditions the 'breaking point' is reached when the CO₂ tension has risen to 6–7% of an atmosphere and the O₂ tension fallen to 9–10%... On breathing the expired air in and out of a small bag, we found that the CO₂ tension rose to about 8% and the O₂ fell to about 8.5–4.5% before the breaking point occurred...

The fact that the tension of CO₂ can be raised by breathing O₂, from 6–7% to 8–10% before the breaking point occurs, led us to try the effect of inhalations of oxygen both on the power to carry on muscular exercise on trained athletes and on untrained persons."

The main conclusion of the 1910 study, summarized by a later commentator, was that "the symptoms of hyperventilation could be largely suppressed by forced breathing of oxygen instead of air." As was common for the era, the experimental subjects were the experimenters, their friends and their colleagues. Here is one example:

"The middle aged men were able to breathe a considerably greater volume of O₂ per minute than of air; for example:

L. H. The numbers... refer to litres in each successive 30 secs.

Air 3 mins.: 24.5, 28.5, 31, 26, 24, 21.5
= 155.5 Face congested, tightness round



head. Held breath afterwards 1 min. 47 secs.

O₂ 3 mins.: 33, 36, 40, 38, 34, 32 = 213
Comfortable. Held breath 6 mins. 2 secs.
Heart throbbing then and sweating
beginning, no distress, desire to breathe
suddenly become imperative.

The L.H. referred to here is Hill himself, then in his early 40s.

Though Hill was a major figure in the physiological world of the time – *inter alia* Professor at the London Hospital, FRS in 1900 aged only 34, secretary of The Physiological Society and later knight – he may be best remembered now as the father of the pioneering medical statistician (Austin) Bradford Hill (1897–1991). Bradford Hill was the mentor and co-author of Richard Doll in the famous epidemiological studies that pinpointed smoking as the major cause of lung cancer. He also set down the 'Bradford Hill criteria' still used to help infer causation in epidemiological studies.

We know much about Leonard Hill's life from a charming memoir written by Bradford Hill and his elder brother Brian in 1968. The Hills were a long-established middle class family, with a tradition in education and running schools. The most famous relative in the generations before Leonard Hill was his great-uncle Rowland Hill (1795–1879), founder of the British postal service. We are told:

"[Leonard's father] decided that his sons should make careers in the professions and each boy was told which ...he should adopt...Leonard's fate was to be medicine, although he would have much preferred, he said, the life of a farmer."

On finishing his studies Hill considered a medical career but instead opted for research, describing it to his future wife as "the path which saves the millions when found."

Like other physiologists of the era, Hill's work ranged over many subjects, but assessments of human physiology and performance were a recurring theme. Following on from some early work on assessing the cerebral circulation

in man, Hill developed in the 1890s, together with HL Barnard, an arm-cuff for blood pressure measurements. His sons report: "He records that he had submitted this paper [describing the apparatus] to the Royal Society but that it was considered unsuitable for publication in their Proceedings as being only an account of an instrument. As a result of the delay he and Barnard lost priority to the Italian worker Riva-Rocci who had independently been working on the same lines." Later Hill did important work on 'caisson disease' (decompression sickness).

At one point in the 1910 paper we learn of L.H. that "pleuritic adhesions on left side [of the chest] have lessened vital capacity from 4.5 to 3.5 litres". These adhesions probably resulted from the respiratory tuberculosis Hill had contracted in 1904, which had necessitated an extended leave of absence and convalescence in the mild climes of the West Country. A second bout of TB followed in 1916. Bradford Hill also contracted TB in 1914 shortly after joining the Flying Corps. The illness got him 'invalided out', and he spent the whole of the war in hospitals or convalescing. Given the attrition rate on WW1 flying crew, this might be judged paradoxically fortunate. However, the family's travails with TB show just what a scourge the disease was, even for the upper middle class of the time. In their memoir, Hill's sons note that the TB caused their father to give up his pipe.

Leonard Hill's later research interests concentrated on the effect of people's working environment on their health, making him a pioneer of modern occupational physiology and medicine. His contemporaries certainly judged him so, with one describing him as "the real founder of applied physiology in England". Hill investigated the air quality and ventilation in the House of Commons; he judged them "just the wrong conditions for legislators"! Hill retained a life-long interest in fitness; his sons tell us he: "practised very much what he preached. For many years while living at Loughton he would be up by six in the morning, bicycle two to three miles through Epping Forest and bathe in a forest pool. And this all the year round." In retirement Hill painted (an accomplished landscape painter, he mounted several successful exhibitions of his work), and kept up a daily 4 mile cliff-top walk until his sudden death from a stroke, aged 85.

Austin Elliott

Hill LE & Flack M (1908). *J Physiol* **37**, 77–111.

Hill AB & Hill B (1968). *Proc R Soc Med* **61**, 307–316.

Parliamentary Links Day – science and the new Parliament

22 June 2010

This annual event, showcasing science for Parliamentarians, is co-ordinated by the Royal Society of Chemistry and regularly draws an audience of high-profile politicians, helped by the involvement of the extremely well-connected Stephen Benn. This year was no exception, and the timing was particularly fortuitous as it was on the morning of the day of the emergency budget discussion. So we were able to engage some political minds on the importance of science just before they rushed off to vote.

Presentations on important issues in science were made by The Royal Society, Royal Academy of Engineering, Royal Society of Chemistry, Institute of Physics, Society of Biology, The Geological Society, Royal Astronomical Society, Institution of Chemical Engineers, and the Campaign for Science and Engineering. The Parliamentary speakers were John Bercow MP (Speaker of the House of Commons), Mark Lancaster MP, Julian Huppert MP, Malcolm Wicks MP (former Minister for Science), David Willetts MP (Minister of State for Universities and Science), Ed Miliband MP (Shadow Secretary of State for Energy and Climate Change), Andrew Miller MP (Chair-elect of the Commons Science and Technology Select Committee), John Beddington (Chief Scientific Advisor), and David Cope (Parliamentary Office of Science and Technology).

Presentations were crammed into a busy morning, too many to go into detail here. Suffice to say that the scientific presenters waxed eloquent on horizons in their various disciplines, and how supporting science, even (and especially) in such difficult economic circumstances, was vital to the UK economy. And the politicians tended to agree. Points that particularly caught my ear from the political end were as follows.

John Bercow hoped that there would be a great leap forward in this Parliament in understanding the vital role of science, but that a lot of work was needed to identify and engage with the many new MPs. Malcolm Wicks stressed the importance of bridging the understanding gap between scientists and politicians to effectively tackle pressing national and global issues such as climate change. David Cope said that the Parliamentary Office of Science and Technology, which exists to

brief Parliament on scientific issues, is currently looking for ideas for briefing papers. Andrew Miller, as new Chair of the Commons Science and Technology Select Committee, is still awaiting the make-up of his committee (we really need to encourage new MPs to take an interest), and sees investment in science as the seed corn for new economic growth. He highlighted the need to involve the public to counter a developing anti-science culture in some quarters. David Willetts noted the departure of many MPs who had taken a strong interest in science such as Evan Harris, Ian Taylor and Ian Gibson. Currently there are 65 MPs with a degree in a STEM subject, and an additional 15 with a potential interest but no formal training in science.

Julian Huppert MP, a member of the Institute of Physics, and until 6th May a working scientist, is a welcome addition to the Commons. He commented that Parliament is a bizarre place for a neophyte MP to get to grips with and compared it with being a first year at Hogwarts. But it is a place that values expertise, something that scientists can build on. The Commons is still short of scientific expertise, a very different state of affairs to the Lords. We need to work on our relations with the public. Also science isn't just about scientific interests; the scientific method is a vital

input to any issue exercising Parliament. John Beddington reinforced this by noting that everywhere you look you see challenges that need to be addressed by scientists. Cross-disciplinary alliances are particularly important to tackle this. One area that needs to be addressed is how to work with social scientists to tackle issues such as obesity and ageing. Scientific evidence is key to developing rational policies, making smarter use of scarce resources. John caused a ripple of merriment around the room when he showed pictures of the Chief Scientific Advisors working in various Government Departments, including a space for the one working in MI5 whose identity cannot be revealed. But people were glad to know that he is there!

A key message from this meeting was the vital importance of doing whatever we can to get new MPs involved, and to make them understand the important role of science. Austin Elliott in his Editorial in the last *Physiology News* 'Who is Listening?' rightly stressed that the answer is to write to your local MP, and covered the issues that need to be addressed. I would recommend that you read it if you haven't already. Whatever the background/interests of your local MP, they all care about what their constituents think of them.

Liz Bell

And just as we were going to Press, on 9th July I was invited to the Royal Institution to see David Willetts deliver his first speech on the Government's vision for science in the UK. The key points I picked up were:

- As Minister he believes in the vital role of science, supporting excellent research, the Haldane Principle and Dual Funding. He also believes that scientific thinking will become increasingly important as a cohesive force in a multicultural society.
- But the country is in serious financial straits. Funding for science under Labour was fuelled by debt-driven growth, so the looming Comprehensive Spending Review is going to have to make some tough choices. The Government is aware that some countries such as the US have chosen to tackle their economic woes by ramping up funding for science, but their public finances are in a better general state than ours.
- Vince Cable *et al.* understand the role of SET in rebalancing the economy.
- Science induction has been offered to new MPs.
- How to use scientific evidence will be in the Ministerial Code.
- Libel Laws will get their much needed overhaul.
- The Office of Life Sciences will continue.
- More needs to be done in the area of vocational training.
- As impacts in science often arise in serendipitous ways, there is no way to perfectly assess this. So he announced the decision to delay the next Research Excellence Framework for a year to try to learn lessons from pilot studies underway.
- In terms of promoting links between science and the broader economy, he believes in supporting clusters such as those in Dundee on life sciences and computer games, and promoting science in more general terms so we have the 'absorptive capacity' to take advantage of research findings wherever they originate. He is also keen on public funding for shared 'research platforms' with industry, using public sector purchasing to leverage innovation and support small and medium sized enterprises (SMEs), and competitions to help drive innovation in technologies we are likely to need e.g. better batteries for hybrid cars.

High jinks at Cheltenham

The Society was very active at the Cheltenham Festival this year, where we were an important sponsor of the meeting through our partners at The Society of Biology. A record number of visitors were at the festival (it seems to grow every year), so it's a good place to be.

We ran an event on asthma in the Town Hall on Friday 11th June, which was very well attended. Or to be strictly accurate we were in a posh tent just outside the Town Hall on a gorgeous sunny day, with a lively audience of over 100 people who had gathered to hear why some of us are struggling for breath, and to explore how research advances might make it possible for sufferers to breathe more easily in future. Nazir Qureshi, who is living with asthma, joined researcher Clive Page and clinician John Price (both from KCL) to outline the main issues and engage in debate with an audience, many of whom showed that the issues were of keen interest to them as patients and families of patients. To experience what restricted breathing feels like,

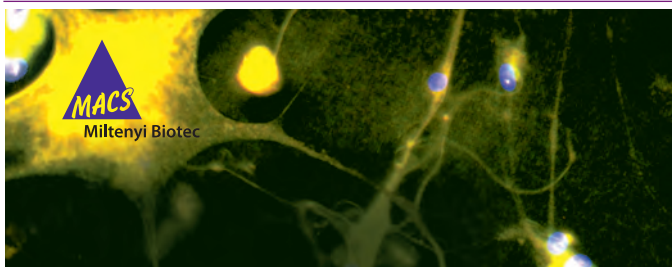


non-asthmatics were invited to try breathing through straws that were handed out to the audience. Our only disappointment, was that, like Cinderella, we had to rush off to get a train, and so missed Clive Page's subsequent event on the science of chocolate, and the chance to win a huge wodge of confectionery!

We also sponsored the attendance of Bristol University's Mobile Teaching Unit, which had The Society's logo emblazoned on the side, further raising our visibility at the Festival. The lorry received a steady stream of visitors for the two days it was there; the volunteer staff were kept busy right up until Kim Healey shut the doors at 5 pm. We had a variety of activities (including ECG, vitalograph, comparative anatomy, making a pipe cleaner neurone, Stroop test and Neurobot) and all were well received. Most of our visitors were families with children.

Our special thanks go to the asthma event speakers, and to Judy Harris, Max Headley, Kim Healey and all the volunteers who made the Mobile Teaching Unit attendance possible.

Liz Bell



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Society update for 2010

Society Officers

At the AGM in July, following the end of their terms of office, Clive Orchard stood down as President and Prem Kumar as Meetings Secretary. The new President of The Society is Mike Spyer, with Jonathan Ashmore as Deputy President. The new Meetings Secretary is David Wyllie.

Executive Committee 2010–2011

President Mike Spyer
Deputy President Jonathan Ashmore
Honorary Treasurer Rod Dimaline
Meetings Secretary David Wyllie
Chair, Education Louise Robson
Chair, External Relations Policy Jeremy Ward
Chair, Publications Ian McGrath

Further information can be found at:
www.physoc.org/governance

Annual General Meeting

The Society's AGM was held on 1 July at the University of Manchester. The minutes of the meeting are available at www.physoc.org/agm

The Physiological Society techniques workshops

Two years ago the Education Committee of The Physiological Society sent out a questionnaire to Members to gather information as to what technique workshops Members had attended previously and what workshops they would like to see supported in the future. We had a great response to the questionnaire and as a result I was given the task, by the Education Committee, to oversee the development of a new set of techniques workshops. The new-format workshops have just finished running for their first year and it seemed a good opportunity to review their success or otherwise and to see whether other workshops should be developed for the future.

The results of The Society's workshop survey demonstrated that Members were keen to have workshops on bioinformatics, imaging, proteomics, *in vivo* techniques, electrophysiology and molecular techniques. These were the top six subject areas, although many other more specific topics were also suggested. Armed with this information, the Education Committee attempted to identify workshops that would provide training in the most frequently requested areas. We were also careful to select a format that would be the most accessible and effective for our membership – choosing to make the workshops modular, each lasting from 1 to 2 days. The idea here was to allow Members to pick and choose modules, allowing them to build up a portfolio of techniques, should they so wish.

The Society already supports an *in vivo* workshop (held each year at Glasgow University, Bristol University and King's College London) and a microelectrode techniques workshop (held at Plymouth), and support for these has recently been renewed for 2009–11. Our main priority was therefore to introduce a new imaging workshop and to create a new modular molecular techniques

Proposed modular format for the new molecular techniques workshop

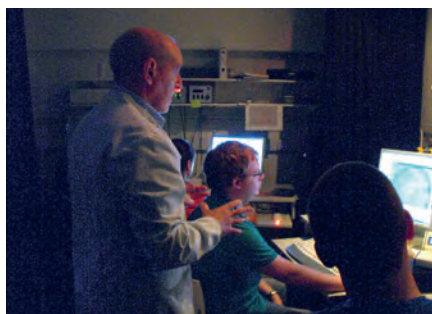
	Name of module	Organiser
Module 1	Introduction to molecular techniques	Patrick Harrison (Cork)
Module 2	Measurement of gene expression using real-time quantitative PCR	David Sugden (KCL) and Patricia de Winter (UCL)
Module 3	Transfections and functional studies	Patrick Harrison (Cork)
Module 4	Bioinformatics	
Module 5	Microarray and gene knockdown (siRNA)	

workshop that would include bioinformatics/proteomics.

The Education Committee approved the development of this modular molecular techniques workshop containing the modules shown above.



Participants on the live-cell imaging workshop at UEA.



Paul Thomas explaining live-cell imaging.

With the help of Members of The Society who have expertise in running workshops in these areas, we have provided the first three modules of the workshop. We have also supported Paul Thomas to run a new Live-cell imaging workshop at the University of East Anglia, Norwich.

Initial feedback from participants from all the workshops (PhD students, post-docs and lecturers) has been really positive. The majority have commented on: how material

covered in workshops has added to previous experience; how workshops were well organised; how workshops were about the right length and good value for money. Participants particularly liked the hands-on experience, which is a hallmark of The Physiological Society techniques workshops.

The Society is looking for Members to assist in the delivery of the outstanding modules of the workshops: Bioinformatics and Microarray and gene knockdown. We hope to be able to run all six modules in 2011.

I hope that in the years to come, The Society will be able to support similar workshops in other areas of the UK, to help with the logistics of Members being able to attend. I also hope that this article will raise awareness of the techniques workshops to the membership. I would be very happy to hear from any Member who would be willing to organise one of these workshops, in particular the Bioinformatics and Microarray and gene knockdown modules.

Places on the 2010 *in vivo* workshop and microelectrode techniques workshop have all been allocated. To find out more about all the 2011 workshops, keep an eye on The Society's website (www.physoc.org/education). If you are interested in running a workshop, in particular those listed above, please email education@physoc.org

John Winpenny
Education Committee
University of East Anglia

YPS at Physiology 2010

On a sunny Monday afternoon in June young physiologists from around the world arrived at the University of Manchester for the Young Physiologists' Symposium (YPS) 'Physiology and disease: advances and perspectives'. The seemingly broad theme of this symposium aimed to encompass the breadth of research areas in physiology, specifically addressing the association between physiology and disease, whilst looking towards areas of future progression.

Upon arrival delegates had the chance to mingle with fellow young scientists over a buffet lunch, whilst discovering the new products the sponsoring companies had to offer.

Martin Humphries, Dean of the University's Faculty of Life Sciences and Vice-President of the University, opened the conference with a short speech emphasising the importance of bringing young scientists together in the less formal setting of a symposium like the YPS. He also highlighted the broad spectrum of science that this meeting had attracted, setting the scene for a fantastic symposium.

The first seminar series was 'Cardiovascular disease'. Plenary speaker Saadeh Sulieman from the University of Bristol gave a fascinating talk entitled 'How to mend a broken heart'; this was followed by four excellent talks from students. The second session covered 'Metabolic disease' and was headed by Patrick Rorsman from Oxford University. This insightful talk considered links between obesity and impairment of insulin secretion that can lead to type II diabetes. The high standard of science continued with four more student talks during this session.

Delegates and speakers were all in high spirits after a stimulating day, and ended up with a fun evening at the symposium dinner, which was held at *Lal Qila* on the famous Curry Mile in Rusholme. Gorging on unlimited curry there was non-stop

chatter and socialising. All four guest speakers were also engaged in conversation with students from start to finish. A trip to the local watering-hole once dinner was done capped off a brilliant evening and it was clear that many new friendships had been formed.



The next day began early, with the late night only seeming to spur on the delegates enthusiasm for more science, and by 9.30am the seminar room was buzzing. Mustafa Djamgoz from Imperial College London kicked things off in the 'Epithelial disease' session with his exciting research on 'Progression of carcinomas by membrane excitability'. The last scientific seminar of the day was 'Neurological disease'. Hugh Perry from Southampton University presented his intriguing work on how systemic inflammation could contribute to chronic neurodegeneration. Again the student talks following the plenaries in both sessions were of excellent calibre.

Delegates, speakers and sponsors were then escorted to the Great Hall in the Sackville Street building for the poster session. A superb lunch was provided whilst posters were being judged. There were 58 posters in total creating a task and a half for the judges.

As the judges considered their preferences, the rest of the conference returned back to University Place for a final workshop hosted by the charity Sense About Science. Julia Wilson from Sense About Science guided delegates through the current work of the charity, which responds to misrepresentation of science and scientific evidence on issues that

matter to the public. This was followed by interesting discussion of specific examples of work by the Voice of Young Science branch of the charity – which is sure to have gained a few more young scientists in its membership as a result.

The end of the conference was celebrated with a drinks reception and prize-giving. The judging panel for the prizes consisted of the four plenary speakers as well as Owen Jones, Donald Ward and Jason Bruce from the University of Manchester. After much deliberation due to the exceptional standard of all presentations the winners were announced as follows:

Best poster presentation: Samantha Lane, University of Bristol

Best oral presentation: Annie Stride, University of Birmingham

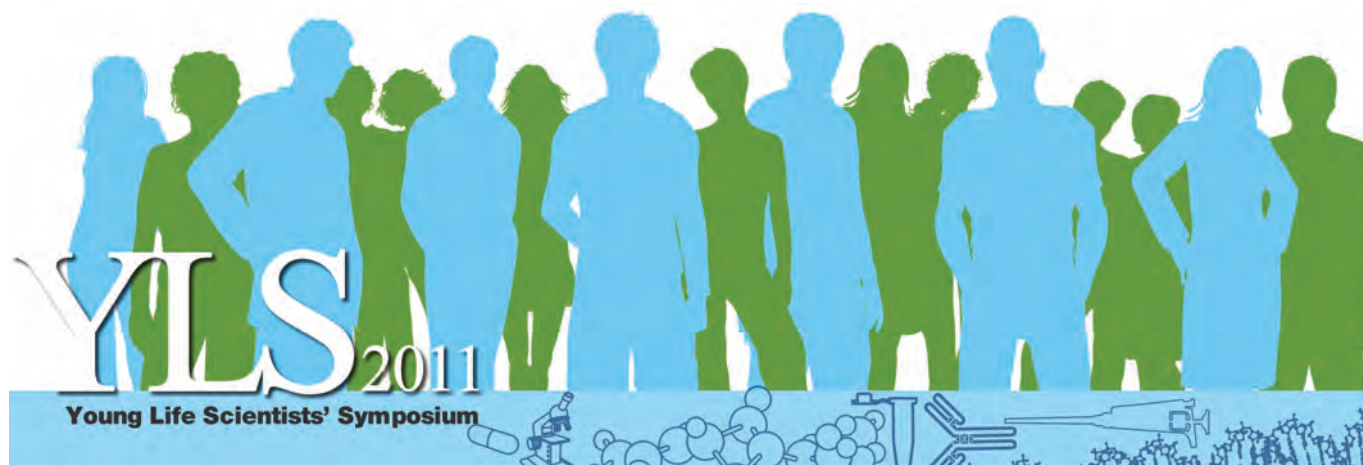
Congratulations to both winners.

That concluded the conference and nicely set up the start of the main Physiological Society meeting. Professor Sulieman summarised his thoughts on YPS after the meeting saying: '*The YPS in Manchester 2010 was a celebration of the outstanding qualities of young physiologists at all levels. The organisation was first class, the research sessions were excellent and the social skills were impressive. The whole exercise was a breath of fresh air. Congratulations.*' Comments from delegates on the Facebook page included '*Had a wonderful time and the Irish contingent were made to feel very welcome! Hope you all enjoyed it as much as we did!*' and '*YPS was an excellent work done by the students of Manchester University*'.

A note of thanks to all the speakers and judges, plus Julia from Sense About Science. A huge thank you also to all the organising committee for the work that has been put in to make this a thoroughly enjoyable YPS.

Parini Mankad

Vice Chair of the organising committee



Young Life Scientists' Symposium 2011

Calling all young life scientists . . .

Are you excited by your area of research, but frustrated by the lack of meetings taking place?

Would you like to organize a scientific conference for your peers aimed at promoting the latest research in your area?

Organizing YLS provides the opportunity to work with the Biochemical Society, the British Pharmacological Society and the Physiological Society in providing emerging scientists the opportunity to network and build new contacts.

Other benefits involve:

- Add experience to your CV
- Develop new skills
- Get a head start on a career in research through conference organization

Applicants must be prepared to work in a team to organize a one day themed symposium, from finding a venue and designing the scientific programme, to marketing the conference, assessing abstracts and raising sponsorship.

To give you an idea of what you could achieve, the website for YLS2010 can be viewed at:
<http://www.asthma-allergy.ac.uk/yls2010/index.html>

Getting involved:

The Societies are looking for a group of four PhD students or Post Docs to be the key organizers of YLS2011. Experienced undergraduates can also apply. Applicants must submit a complete meeting proposal, include a CV for each applicant and a letter of support from supervisors, by 24 September 2010.

To find out more about YLS and further application details, please contact education@biochemistry.org or visit www.biochemistry.org/Education/Events

Mary Cotter awarded the first Otto Hutter Physiology Teaching Prize at Physiology 2010

Teaching is becoming an increasingly high-profile activity at The Physiological Society, and this was obvious at the Main Meeting of The Society in Manchester.

At the teaching symposium, entitled 'The sustainability of physiology teaching and teachers', we were proud to award the first Otto Hutter Physiology Teaching Prize to Professor Mary Cotter of the University of Aberdeen. Although Professor Hutter wasn't able to attend the meeting, he did send some kind words of congratulations to Mary to acknowledge her achievements.

The Society was pleased that Professor Cotter was available to collect her prize and also to contribute to the symposium. In her presentation, 'Physiology: simply the best', Mary shared some of the innovative teaching methods that she has found effective in physiology



Mary receiving the prize from Louise Robson.

teaching; indeed, Mary's ability to engage an audience was proven as she illustrated the benefits of the Personal Response System (PRS) handsets. The handsets allow students to gain instant but anonymous feedback, whilst also comparing their level of ability within a class – the anonymity was much welcomed as some members

of a room full of physiologists failed to provide the correct responses to some basic physiological questions!

Delegates from the UK and abroad who attended Physiology 2010 agreed that the Teaching Prize is an important step forward in acknowledging the role of teachers in the physiology (and wider biomedical) community.

If you would like to make a nomination for the 2010 Otto Hutter Physiology Teaching Prize, please go to The Society's website (www.physoc.org/education) or contact education@physoc.org. The deadline for nominations is **30 September 2010**.

The Benevolent Fund

The 2010 Ben Fund Raffle raised £332 at the Main Meeting in Manchester. Many thanks to all those who bought tickets.

The lucky winner was Alan Noble from Southampton.

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Ask a physiologist!

Why do we have both burping and farting? Robin (11)

Dr Patricia de Winter, University College London, replies:

Gases emitted from burping and farting are different in origin. Burping, or eructation, to give it its medical name, is simply the escape of air from the stomach. When we eat or drink we swallow air as well as food or liquid and an excess of air may escape as a burp. This happens more often if you eat too quickly or drink gassy liquids. Some of the air we take in from eating and drinking exits the stomach and passes into the intestines. A fart, more formally known as flatulence, is the escape of gas mixtures from the large intestine, via the rectum. The gas mixture originates from two sources: some is from swallowed air and some is produced by microorganisms, such as yeast and bacteria, that live in our gut. I'm sure you have realised by now that eating certain foods produces more flatulence than others, for example beans and pulses often result in flatulence. This is because these foods arrive in the bowel only partly digested and the gut microorganisms finish off the job, producing flatus gases in the process.

If you imagine the world was made and ended in a day, how much of the day would we take up? Amelia (11)

Dr Patricia de Winter, University College London, replies:

The earth is around 4.54 billion years old (4,540,000,000 years) and modern human species have been around for about 300,000 years, and even less if you include only our subspecies *Homo sapiens sapiens* (very modern humans). So if the history of the world were to be represented in 24 hours, humans would be around for less than the very last second of the day.

Why do humans need to sleep? Conor (17)

Dr David Sugden, King's College London replies:

After many decades of research there is still much debate about the function of sleep. Everyone would acknowledge that a good night's sleep makes you feel more alert, energetic and better able to function. Lack of sleep has clear consequences; it not only makes you grumpy in the morning, but also impairs concentration and performance, can disturb vision and slow reaction time. Chronic sleep disturbance can reduce immune function and increase the risk of obesity, diabetes and cardiovascular disease.

It seems likely that no single theory will explain why we sleep, though several have been proposed. One of the earliest ideas – the adaptive or evolutionary theory – suggested that sleep evolved as a survival strategy to keep an animal away from harm at vulnerable times, for example in darkness or when predators were active. However, it seems logical to suppose that remaining conscious – if inactive – might prove a safer policy. A related idea proposes that sleep is a mechanism to allow an individual to reduce energy expenditure, perhaps at times when the search for food is least likely to be successful. Other theories have been proposed that suggest that sleep allows the body and brain to repair and replenish themselves. Activities associated with restoration such as growth hormone secretion, and protein synthesis occur during sleep, and babies (if you're lucky!) sleep lots. Sleep plays a critical role in brain plasticity not only in infants but also in adults as well, and research indicates that sleep quantity and quality can have an important influence on learning and memory.

To learn more about this topic I recommend this excellent web site: <http://healthysleep.med.harvard.edu/>

How does an ostrich know what it is doing when its eyes are bigger than its brain? Amber (11)

Dr Charles Deeming, University of Lincoln, replies:

Ostrich eyes are indeed large (it is the biggest bird eye and is even larger than that of many large mammals), and bigger than their brains but this does not make them stupid, however. It is not a case of an undersized brain but rather of oversized eyes. Bird brains are generally smaller than in mammals of the same body mass but this reflects the different emphases on sensory perception (such as vision) and the need to process this information. Ostrich brains may be small compared to the bird but they are more than adequate to allow the bird to sense and respond to the environment in a variety of sophisticated behaviours. Their eyes are, by contrast, very large and provide fantastic eyesight that allows ostriches to see threats and food from a great distance. An ostrich's eyes are a real asset and far from hindering the bird's behaviour they actually help it in its everyday life.

Erratum

In the previous issue (PN 79) p. 45, the sentence:

“‘Semantic memory’ is our ability to recall facts e.g. giraffes come from Africa, and the basal ganglia and cerebellum are important for this’ was unfortunately edited incorrectly. The text should have read:

“‘Semantic memory’ is to do with our ability to remember and recall facts e.g. giraffes come from Africa. Learning a skill, such as riding a bike, is also a type of memory. In this example you are able to learn to identify a bike (an example of semantic memory) before you are able to learn the skill of riding it. Regions such as the basal ganglia and cerebellum are important for learning motor skills.’

The Journal of Physiology

Experimental Physiology

Translation and Integration

New Editor for 2010



John R Halliwill, Associate Professor of Human Physiology, University of Oregon.

John Halliwill is a leading researcher on why blood pressure is lower after exercise (post-exercise hypotension). He is a Fellow of the American College of Sports Medicine and has received awards from the American Physiological Society and the *Journal of Applied Physiology*.

Throughout his career, John's research has focused on identifying the hormonal, neural or metabolic factors that are responsible for changes in the cardiovascular system during exposure to environmental and physical stresses. He has studied astronauts and worked with Olympians and the US Marines. "We learn much more about the cardiovascular system when we challenge it. Just sitting around, we won't know what it is capable of doing. Push it with a stress such as exercise or altitude, and we get to see how robust a system it is, we gain insight into what can go wrong, and we can catch a glimpse of what disease is all about. And as we say informally, but in all sincerity in the lab, 'We've been stressing people out since 2002'"

John graduated with a BS degree in Zoology from The Ohio State University in 1991. In 1995, he received his doctorate in physiology from the Medical College of Virginia. He subsequently trained as a post-doctoral fellow at the Mayo Clinic and Foundation, until his appointment to the clinic's staff as an assistant professor of

anesthesiology in 1999. In 2002, John joined the University of Oregon's Department of Human Physiology. He co-directs the Evonuk Environmental Physiology Core and the Bowerman Sports Science Clinic.

The Journal of Physiology Sponsored meetings and Symposia for 2010

Reactive oxygen and nitrogen species in skeletal muscle: acute and long-term effects

Satellite symposium at the XXXIX European Muscle Conference 2010, Padua, Italy, 11 September

Chair, organiser and speakers:
Roberto Bottinelli, Håkan Westerblad, Scott Powers, Graham Lamb, John M Lawler, Michael J Jackson, Michael B Reid

TRP channels: from structure to disease

Festschrift in honour of Bernd Nilius
Leuven, 23–25 September

Chair and speakers: Thomas Voets, Rachelle Gaudet, Giovanni Appendino, Ardem Patapoutian, Rudi Vennekens, Rene Bindels, Reinhold Penner, David Julius, Thomas Gudermann, Stuart Bevan, Lutz Birnbaumer, David Clapham, Sven-Eric Jordt, Craig Montell, Dan Cohn, Bernd Nilius

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Microcircuit-specific processing in the hippocampus

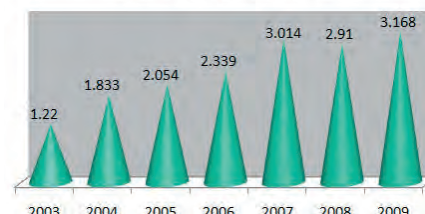
Satellite symposium at Society for Neuroscience, 12 November

Organising Editor and speakers:
Gianmaria Maccaferri, Jeff Magee, Marco Capogna, Doug Coulter and John Lisman

For full details of this, and other symposia visit <http://jp.physoc.org>

Experimental Physiology saw an increase in the Impact factor for 2009 taking it to over 3 and making it a serious competitor to some of the *American Physiological Society* journal titles.

Rising Impact Factor



The journal was ranked 7th out of 75 physiology journals in the Immediacy Index (which measures citations to an article during its first year of publication) indicating that EP articles attract immediate interest.

Increasing journal size

It has been policy to restrict the page allocation against increasing submissions to lead to publication of higher-quality articles. Limited page availability is now leading to the delayed publication of accepted articles in an issue (online publication of individual articles is not delayed) and restricting Editorial policy on invited/scheduled content. Therefore 2011 page allocation will be increased from 1200 to 1352. The current high standard for acceptance will be maintained.

Experimental Physiology at Physiology 2010 Manchester

Experimental Physiology welcomed Editors to Physiology 2010 for their annual UK Board Meeting, where they were pleased to be able to support a number of journal-related events.

The 2010 Paton Lecture



From left to right: Julian Paton, Murray Esler and David Paterson.

The Paton lecturer is invited annually by the *Experimental Physiology* Editorial Board in conjunction with the History and Archives Committee to speak on an aspect of physiology in a historical perspective. This year the invited lecturer was **Murray Esler** who spoke on *The sympathetic nervous system through the ages: from Thomas Willis to resistant hypertension*.

It will be published in *Experimental Physiology* later in the year.

The Inaugural *Experimental Physiology* **Early Career Author's Prize** was presented. The joint winners were Peter Rasmussen and Patrice Brassard, and the runner up was Daniel Breseghello Zoccal. The winning research articles were:

Evidence for a release of BDNF from the brain during exercise
<http://ep.physoc.org/content/94/10/1062.full>

Sympathetic-mediated hypertension of awake juvenile rats submitted to chronic intermittent hypoxia is not linked to baroreflex dysfunction
<http://ep.physoc.org/content/94/9/972.full>



From left to right: Daniel Breseghello Zoccal and Peter Rasmussen pictured with Paton Lecturer Murray Esler.

Full details of the prize and eligibility for entry are online at <http://ep.physoc.org/site/include/files/news1.xhtml>

Experimental Physiology sponsored the symposium *Glial-neuronal interactions in the central nervous cardiovascular and respiratory control*, organised by Sergey Kasparov and Alexander Gourine (Bristol and UCL)

Reports from contributors at this and the symposium *Exercise metabolism in skeletal muscle – from fuel to structure*, organised by Fleming Dela (Copenhagen), will be published in *Experimental Physiology* later this year.

Arriving at a solution

At the end of June *PLoS Biology* published an editorial announcing a new set of guidelines providing explicit and unequivocal instructions on reporting animal experiments – the ARRIVE (Animals in research: reporting *in vivo* experiments) guidelines. The process of generating the guidelines was led by the independent, but predominantly government funded, National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) and the guidelines were developed by a working group including scientists, statisticians, journal editors and research funders.

The Society supports efforts to improve the reporting of research involving animal experiments and has actively backed the guidelines by re-publishing them (by agreement with *PLoS Biology*) in both *The Journal of Physiology* and *Experimental Physiology*, together with a supporting editorial. Other journals have signalled their support in the same way. Both journals now refer authors to the ARRIVE guidelines and we hope that over time these new improved standards of reporting will become the norm.

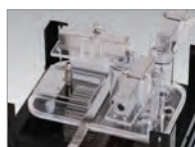


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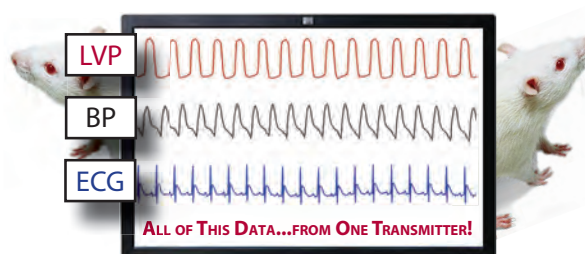
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Richard Darwin Keynes

1919–2010

Richard Keynes died peacefully at home, ending a long and successful career as a university academic, in the international promotion of science, and as a cell physiologist. He was born in 1919, the eldest son of the surgeon and bibliographer Sir Geoffrey Keynes and of Margaret Darwin. He was educated at Oundle School and won a Scholarship to read physical sciences at Trinity College, Cambridge. He added physiology to his first year subjects thus beginning the central interest of his eventual scientific career. He interrupted his university studies to work on sonar at HM Anti-submarine Experimental Establishment and centimetric radar at the Admiralty Signals Establishment during the Second World War, before returning to Cambridge in 1945 to read Part II Physiology and begin a research career in physiology. He became research fellow at Trinity College, teaching fellow at Peterhouse and University Lecturer in Physiology between 1948 and 1960. He then joined the Agricultural Research Council Institute of Animal Physiology at Babraham, becoming its Director in 1965, contributing much to the development of its high international reputation. This would probably not have been achieved with a less energetic individual whom the Agricultural Research Council might sometimes have preferred. He finally returned to Cambridge in 1973 as Professor of Physiology.



Richard Keynes at his desk in the Physiological Laboratory, Cambridge.

Both this energy and exuberance, and his distinguished lineages, are reflected in his life and achievements within and beyond the physiological field. These included his passion for collecting and natural history, and his attachment to and fascination with South America, where, like Darwin, he did some of his most important work. His physiological contributions represent a broad sweep of interests through a range of strategic areas. They extended well beyond the electrophysiological studies in excitable membranes that eventually formed his principal interest.

Within physiology, Keynes was amongst the first researchers successfully to apply radioactive tracer measurements in studies of ionic movements across membranes of living cells. He began these studies

when such techniques were in their infancy, and developed several novel quantitative methods in collaboration with Peter Lewis. They used an ancient cyclotron in the Cavendish Laboratory to bombard appropriate targets with neutrons, and improvised methods to purify the resulting isotopes. This led to one of the most important contributions to biology: the direct demonstration relating nerve impulses in squid giant axon to sodium ion influx (Fig. 1) and potassium ion efflux across the nerve membrane. This directly supported the analysis of the nerve impulse by Alan Hodgkin and Andrew Huxley that later led to their Nobel prize. It was during this period that he also began work demonstrating how the underlying ionic concentration gradients for these fluxes were maintained, through an energy-consuming biochemical process, later to be known as the sodium pump (Fig. 2).

Keynes pursued his scientific interests not only through his many administrative and teaching duties but also in the course of his manifold activities in international science and laboratories overseas. Over a three-month period in Rio de Janeiro in 1951, during his first visit to South America, he clarified the mechanisms, in electrophysiological terms, by which the electric eel *Electrophorus* generates the massive shock that stuns or kills its prey, together with Hugo Martins-Ferreira. This confirmed conjectures made by the physicist Alessandro Volta 150 years earlier. A change in ionic permeability causes the membrane of one surface of each muscle cell within the electrical organ to reverse its resting potential whereas the other surface remains unchanged. This leads to effects akin to deposition of a large charge across the plates of a capacitor, in this case leading to development of potential differences of about 1/6 of a volt across each plate. Arrangements of several thousand such plates in series results in the capacity to generate a powerful electric shock.

At Babraham, Keynes combined a heavy administrative load with an active research programme that included measurements of

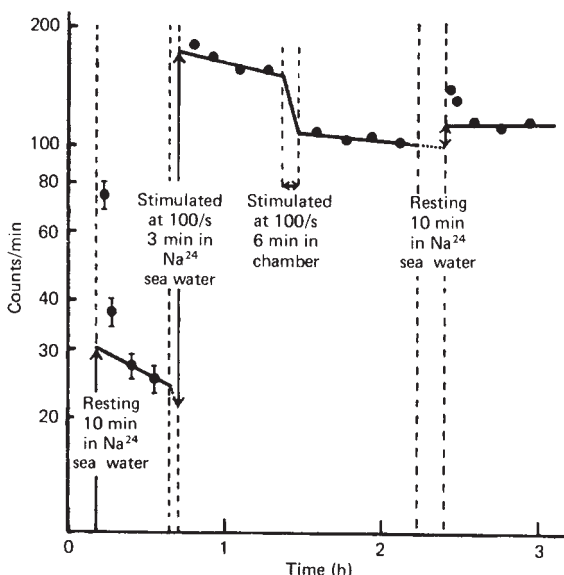


Figure 1. Geiger counter readings following ^{24}Na fluxes in a stimulated *Sepia* axon alternately exposed to ^{24}Na -containing, and inactive sea water. The loss of counts during the first 10 min after exposure to ^{24}Na resulted from washing away of extracellular Na^+ , and was ignored. 1 count/min is equivalent to 42.5×10^{-12} mol Na (cm axon) $^{-1}$. (From Keynes RD (1951). The ionic movements during nervous activity. *J Physiol* 114, 119–150.)

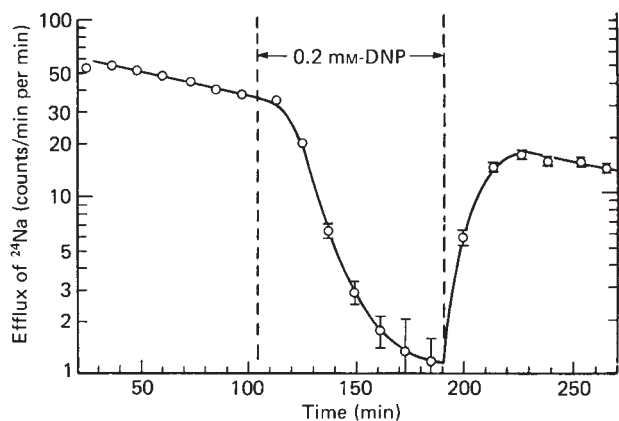


Figure 2. Reversible effect on ^{24}Na efflux produced by the metabolic blocker dinitrophenol in *Sepia* axon. (From Hodgkin AL & Keynes RD (1955). Active transport of cations in giant axons from *Sepia* and *Loligo*. *J Physiol* 128, 28–60.)



Richard dissection the giant axon of *Loligo* in the Marine Biological Laboratory, Plymouth.

thermodynamic, and membrane light scattering and birefringence changes during activity in nerve and electric organs. This formed a broad front of interests combined with studies on ion transport across secretory epithelia, that extended to work on ruminal epithelial potassium transport, thermoregulation and metabolism in sheep.

Back at Cambridge, Keynes managed to carry out his administrative and teaching duties as head of department while resuming his early interests in biophysical properties of nerve membranes. These involved laboratory work during vacations at Plymouth where he dissected giant axons from mantles of freshly caught squid (*Loligo*), for electrophysiological study. This probably represented the one of his many activities in which he was the most absorbed and happy. The work extended concepts bearing on the mechanisms of ion movements across nerve membranes to the molecular level.

Working with Eduardo Rojas, further technical advances were made that permitted direct measurements of the 'gating currents' generated by conformational changes in the sodium channel molecule associated with channel activation, interests he continued to pursue after retirement (Fig. 3).

Keynes complemented his scientific pursuits with keen interests in Darwin's zoological research, particularly those he pursued on the voyage of the *Beagle*, prompted by sketches he discovered by the ship's artist in 1965. This led to publication over the following 35 years of *The Beagle Record* (1979), *Darwin's Beagle Diary* (1988) and his *Zoology Notes from HMS Beagle* (2000). He also supported science for the conservation of Galapagos, in the 1980s and 1990s. He served on the Executive Council of the Charles Darwin Foundation for Galapagos and the Board of the Galapagos Conservation Trust. At the time of

his death, he had just completed work on the 4th edition of his undergraduate book *Nerve and Muscle* in collaboration with Chris Huang.

Keynes was elected Fellow of the Royal Society in 1959, and was a Vice-President from 1965 to 1968. He was elected a Fellow of Churchill College, Cambridge, in 1961 and was a Fellow of Eton College from 1963 to 1978. His international scientific activities led him to becoming Secretary General (1972) then President (1981–84) of the International Union for Pure and Applied Biophysics. He participated in establishing the ICSU/Unesco International Biosciences Networks in the 1980s, later becoming its Chairman (1982–1993). For all these activities he received the Order of Scientific Merit (Brazil) and Honorary Membership of the Latin American Academy of Sciences amongst many academic honours, and was awarded the CBE in 1984. He became a Member of The Physiological Society in 1948 and an Honorary Member in 1993. He served on the Committee (1961–65) and was an Editor for *The Journal of Physiology* (1954–61).

Keynes married Anne Adrian, daughter of Lord Adrian in 1945. They had four sons (of whom the eldest died in 1974). Many will have fond memories of visiting their home in north Norfolk and enjoying sailing trips in Keynes's sailing dinghy *Electrophorus*.

Christopher L-H Huang
Professor of Cell Physiology,
Physiological Laboratory, Cambridge

I would like to thank Professor Roger Keynes for access to historical material in the preparation of this obituary.

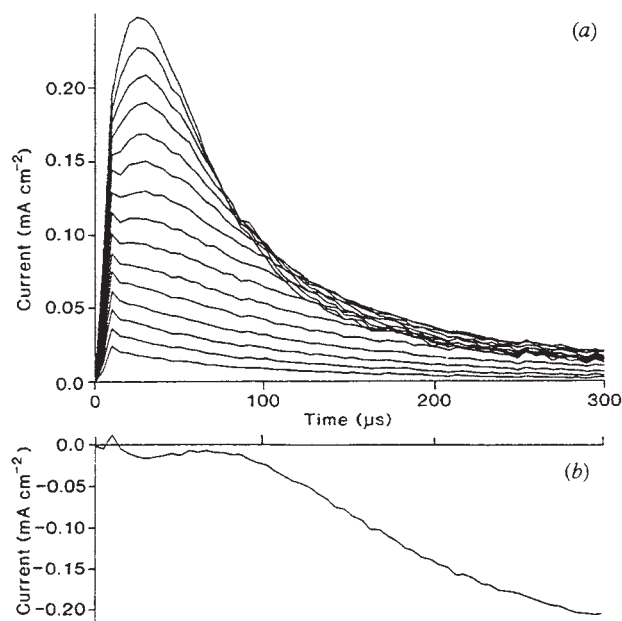
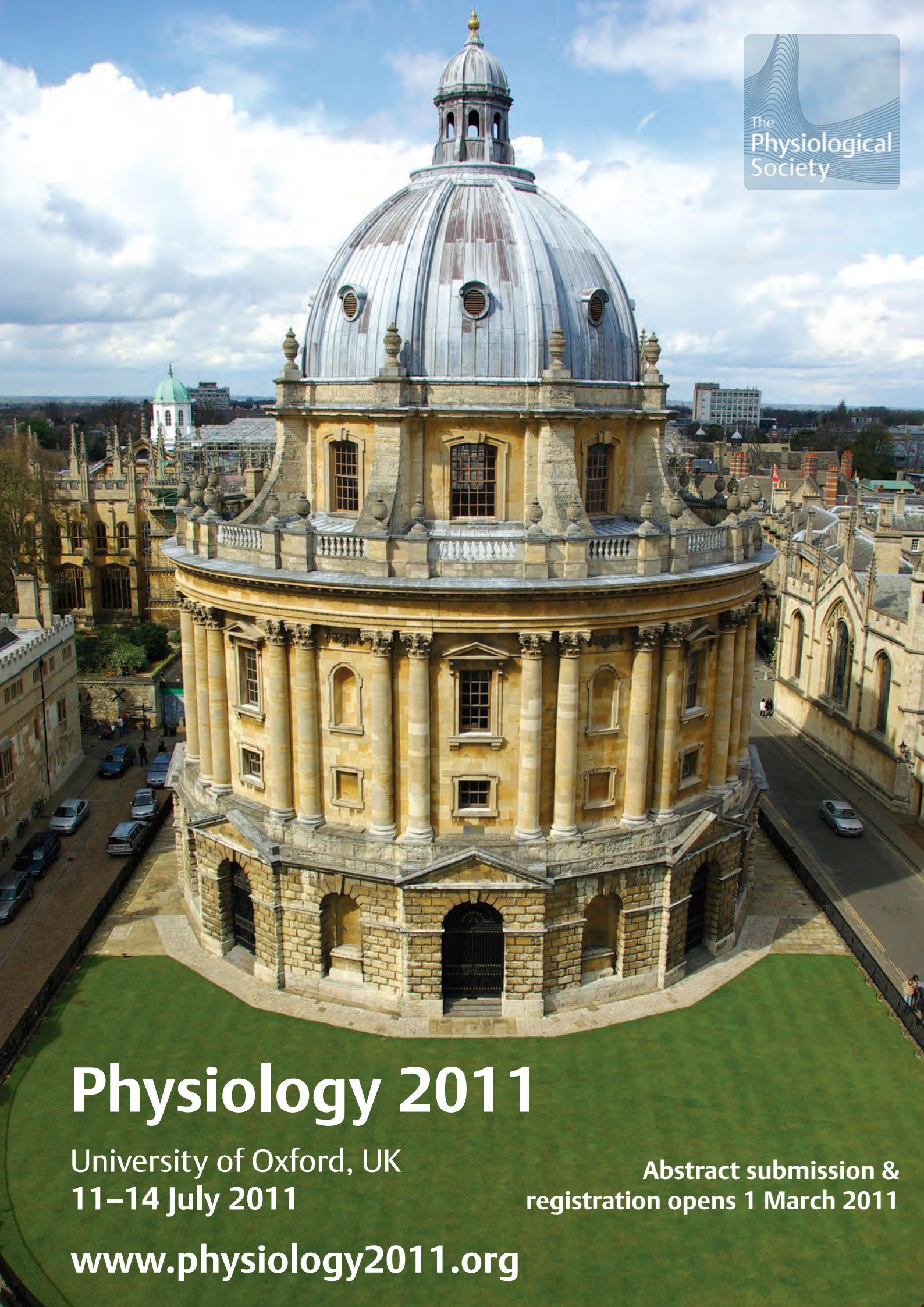


Figure 3. a, averaged sodium gating currents in response to pulses from -80 to between -57 and $+83$ mV from a tetramethylammonium fluoride dialysed squid axon bathed in sodium-free, tetrodotoxin-containing artificial sea water, compared to (b) the initial rise of sodium current following a pulse to -23 mV. (From Keynes RD & Elinder F (1998). On the slowly rising phase of the sodium gating current in the squid giant axon. *Proc R Soc Lond B* 265, 255–262.)

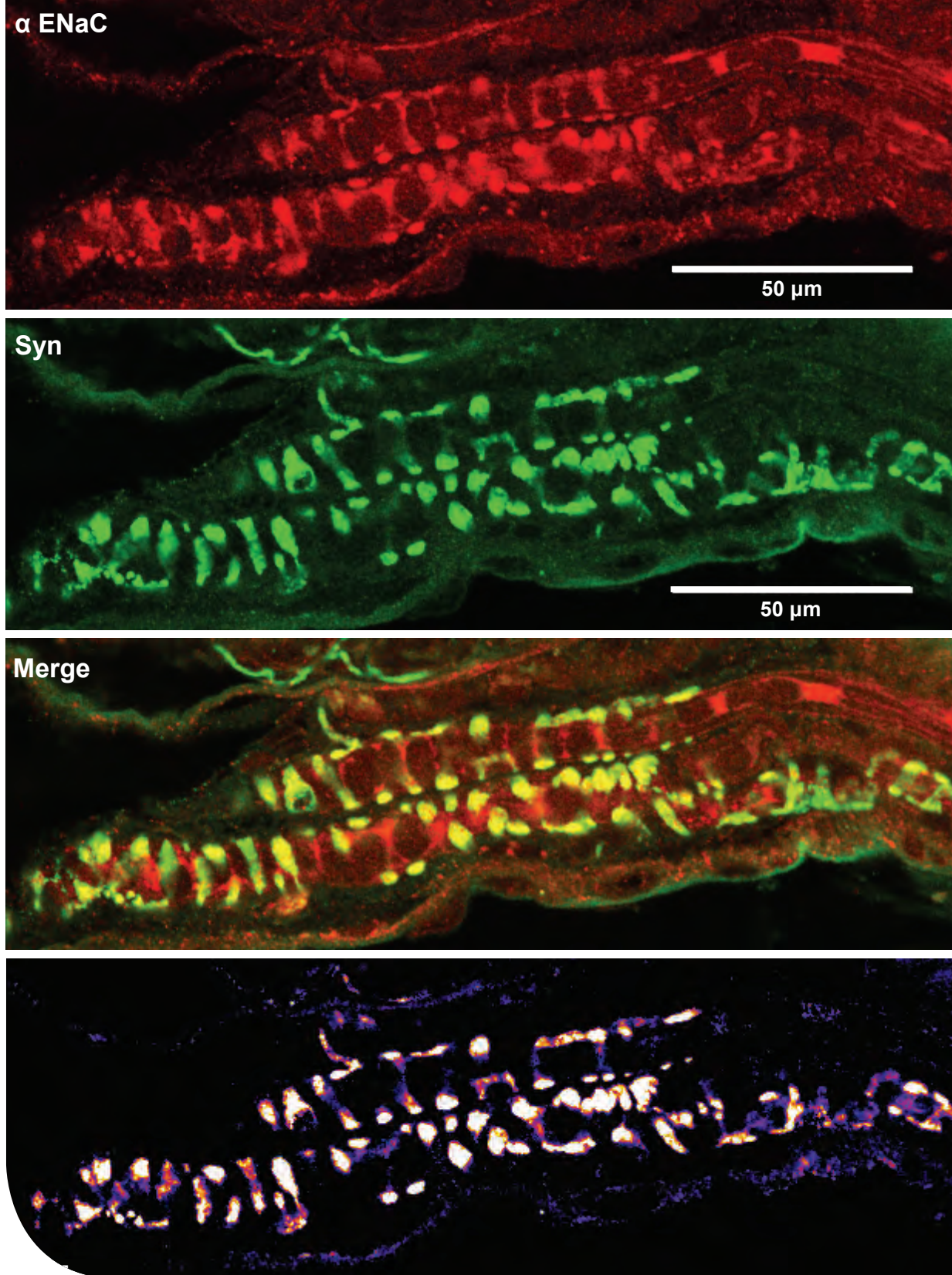


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ASIC2 colocalisation with synaptophysin (p. 34).