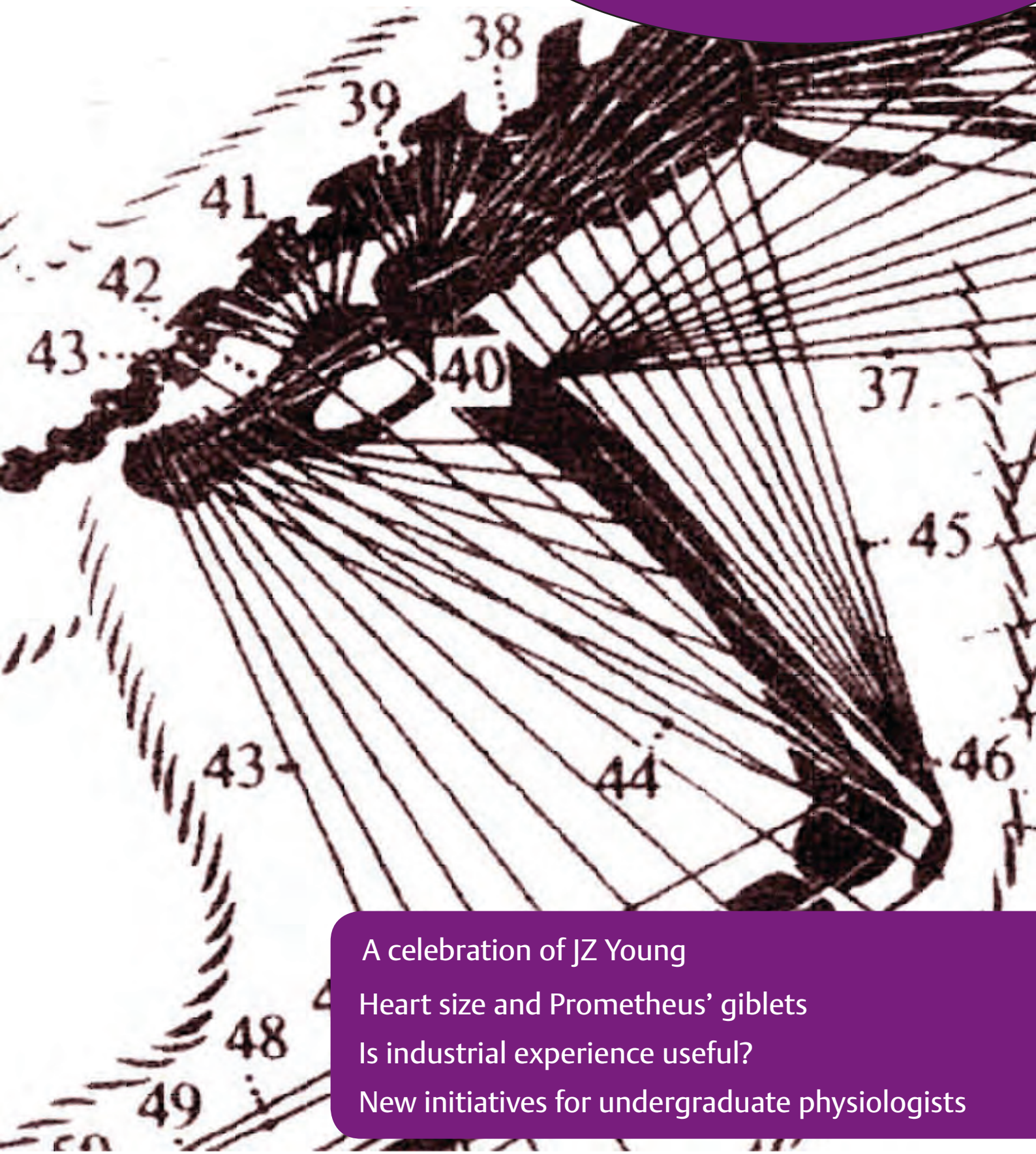
PHYSIOLOGY NEWS

winter 2010 I number 78



A celebration of JZ Young

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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'

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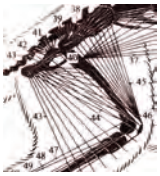
Advancing the science of life



Cover image: The original drawing of the rabbit in *Life of Mammals* by JZ Young, p.34.

PHYSIOLOGY NEWS

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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:
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Physiology News

Deadlines
Letters and articles and all other contributions for inclusion in the Summer 2010 issue, No. 79, should reach the Publications Office (magazine@physoc.org) by **22 April 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
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, 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 Journal of Physiology* style (see *Information and Guidance for Authors:* http://jp.physoc.org).

In this issue
Welcome to the first *Physiology News* of a new decade.

Looking over the News and Views articles, there seems to be something of a 'back to basics' theme going on, with articles concerning either moving, or eating or growing. I am hoping that next time we will have some reproduction and some sleeping to complete the set.

On a historical theme, we feature two of the most singular figures of 20th century biology, both better known by their initials than their names. They are JZ Young, remembered by Fabio DeSio and Andrew Packard on p. 32, and AV Hill, who described the famous Hill equation in *The Journal of Physiology* 100 years ago (p. 35).

This issue also see a slight re-launch of our Education section. It is a truism (or at least something often mentioned by ageing scientists, including editors) that scientific disciplines rise or fall by how well they manage to get young people interested, and keep them interested, in pursuing education, training and research in the subject. To that end we have a range of features looking at physiology education in universities (pp. 44–50), including how to form a student physiology society (p. 47). We also have a new feature, Ask a Physiologist (p. 43), where sixth form students can pose questions for answering by Members (volunteers to answer questions welcome!).

I like to think that JZ and AV would have approved.

Science, engineering and the general election

Making sure that science and engineering are seen as election issues has been the focus of our recent work at the Campaign for Science & Engineering (CaSE). It might be thought that such areas should be apolitical – logic and rational analysis should lead you forward. But in reality, science is rarely so decisive and even when it is, the government needs to implement policies that fit into our political, financial and ethical world.

In fact, CaSE works mostly on policies that affect science, engineering and related subjects, campaigning to improve how they are taught, how research is funded, how government draws upon expert advice, and how it organises their place in government. All clearly political issues.

It is vital that science and engineering policies are clearly spelled out in manifestos for the electorate before they vote. There are over 3 million graduates in science, engineering and related subjects in the workforce who will want to know that their concerns are taken seriously. And the general public is becoming more and more interested in these subjects. It is impossible to ignore their importance in shaping the UK's responses to both national challenges, like rebalancing the economy, and global ones, like climate change.

Over the last six months or so, we have been working with our members, including The Physiological Society, and other collaborators, sharing information and pooling resources. CaSE has been meeting with politicians and their advisors to discuss a range of issues that we hope will be covered in the election manifestos.

As part of this work, CaSE organised a science and engineering policy debate between Lord Drayson, Minister for Science and Innovation, his Conservative Shadow, Adam Afriyie MP, and the Liberal Democrats' Science Spokesman, Dr Evan Harris MP, on January 13th. They were asked questions on a range of topics including: funding, impact and the ring fence; support for industry and research charities; and education.

The debate provided a great opportunity for the audience to see what discriminated the speakers and for the speakers to hear and feel the audience's concerns. Please find a summary and links to the webcast on the CaSE website and blog. It is well worth a watch, not just for its political content. It was a lively evening chaired by Roger Highfield, Editor of New Scientist, with many entertaining, and some decidedly unexpected, moments.

It is worth appreciating the interest which the event provoked. Despite the snow that day, 350 people turned out, with a further 140 watching live online and hundreds of comments on twitter. Within a week, the debate was viewed on the web 1300 times. The point is that people care. Science and engineering policies matter to people far outside Whitehall.

It is only to be expected that the science spokesmen will discuss science policy, but we want to hear commitments from the party leaders too. The Prime Minister was the first to give a speech on science in February 2009. He was followed, just a few weeks ago, by the Liberal Democrat leader, Nick Clegg. David Cameron has yet to make a major speech on science, although he has mentioned it and its role in re-balancing the economy. We are very keen to hear a dedicated speech from him. CaSE will also be writing to the party leaders asking them how their party will respond to the key challenges facing science and engineering in the UK.

As we continue to move science and engineering up the political agenda, it will give the politicians concerned about science and engineering a stronger case to fight for improved policies and funding. And the more that the electorate show that they care, the more forceful that case becomes.

Our blog, CaSE Notes, details the different parties' commitments and links to many other resources. Sign-up to our e-bulletin and follow us on twitter to keep up to date. The Physiological Society is a member of CaSE, but we would be delighted to welcome you as an individual member too.

There is also much that you can do directly. Write to your local prospective parliamentary candidates, in fact, write or comment on the issues wherever you can, from blogs to letters to the local or national press. You could ask questions about science and engineering on radio or television programmes, or at your local hustings, or even organise your own, if necessary.

Politicians have been asked to prioritise science and engineering in their policy-making, please play your part in encouraging and supporting them to do this.

Hilary Leevers
Campaign for Science & Engineering

www.sciencecampaign.org.uk
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Towards an understanding of the enteroendocrine system

Metabolism and Endocrinology Themed Meeting, AstraZeneca, 24–26 March

An increasing amount of information is appearing on the role of the incretin effect in the modulation of many biological mechanisms such as food intake, insulin secretion, metabolism and even cardiovascular actions. It is very timely to try and bring together scientists in this exciting area to review developments.

Bariatric surgery, such as Roux-en-Y gastric bypass, has shown that there are rapid beneficial effects upon type 2 diabetes often before the weight loss effects have been seen. The rapidity of response strongly suggests a gut endocrine effect. It is already known that the incretin effect during a glucose challenge or meal time is blunted in type 2 diabetes and can be enhanced by gastric bypass surgery. The two main incretins, glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), are secreted by endocrine cells of the intestine in response to food and have a wide range of powerful systemic effects. GLP-1 therapies are being utilised in the treatment of type 2 diabetes and obesity with the development of stable GLP-1 analogues. The gut mucosa also contains cells responsible for secretion of other hormones such as ghrelin, peptide YY (PYY) and cholecystokinin (CCK), which can also influence energy balance. There may be many more novel ones still to be discovered.

The symposium will take place over five half-day themed sessions with a total of thirteen invited speakers. In addition there will be oral and poster communications. The symposium will aim to provide a broad spectrum of knowledge on the gut endocrine system from both a cellular and a whole-organism approach so should have a wide appeal. By the end of the meeting we would expect attendees to have been exposed to a thorough discussion of the role of the enteroendocrine system and how it integrates nutrient handling.

The meeting will be held in the recently opened Conference Centre of AstraZeneca Pharmaceuticals at Alderley Park, Cheshire. Alderley Park, which is set in 400 acres of parkland 14 miles south of Manchester, has been the site of pharmaceutical research since 1957 and has seen the development of novel drugs, particularly in the cardiovascular and oncology areas.

Late registration deadline 10 March 2010.

Invited Symposium Speakers

Carlos Diéguez
University of Santiago de Compostela, Spain

Josep Vidal
Hospital Clinic Universitari, Barcelona, Spain

Soraya Shirazi-Beechey
University of Liverpool, UK

Jens Holst
Panum Institute, Copenhagen, Denmark

Rachel Batterham
University College London, UK

John McLaughlin
Hope Hospital, Manchester, UK

Graham Dockray
University of Liverpool, UK

Pat Brubaker
University of Toronto, Canada

Steve Bloom
Imperial College, London, UK

Fiona Gribble
University of Cambridge, UK

Frank Sundler
University of Lund, Sweden

Rémy Burcelin
INSERM, Toulouse, France

Peter Flatt
University of Ulster, UK

Physiology News questionnaire

Tell us your views on *Physiology News* and win an Acer netbook

We are keen to hear what you think of *Physiology News* – too much of something, not enough of another? Fill in our short survey and one lucky respondent will receive an electronic notebook – if you want to be entered for the draw please make sure you include your email address or membership number.

http://www.surveymonkey.com/s/magsurvey

Sensory processing: from transduction to behaviour – the first Cellular & Integrative Neuroscience Themed Meeting at Cardiff University

The Physiological Society held its first Cellular & Integrative Neuroscience Themed Meeting at Cardiff University from 14–16 December 2009. The meeting featured a focused symposium on 'Sensory processing: from transduction to behaviour' with an excellent line-up of 18 invited speakers from the UK and abroad. The programme also included 20 oral communications and 44 poster presentations. The meeting was organised by the Bristol Cardiff Neuroscience Collaboration (BCNC), represented by Frank Sengpiel (Cardiff University), Richard Apps and Bridget Lumb (both University of Bristol).

The meeting attracted 147 registered participants as well as five exhibitors whose sponsorship is much appreciated. The meeting consisted of five half-day sessions, each of them dealing with sensory processing at a different level, from the sensory organs to behavioural output, and between them covering all five senses. We kicked off with a session on sensory transduction, including talks on mechanoreceptor neurons in the skin (Gary Lewin, Max Delbrück Center, Berlin), outer hair cells in the cochlea (Helen Kennedy, University of Bristol), rod and cone photoreceptors (Hugh Matthews, University of Cambridge) and sensory neurons in the mammalian olfactory epithelium (Hiroaki Matsunami, Duke University, USA). In the afternoon of day one, three talks on subcortical processing covered a wide range of topics, from the development of brainstem pain control systems (Maria Fitzgerald, UCL) to thalamocortical interactions in the processing of visual information (Adam Sillito, UCL Institute of Ophthalmology) and the coding of sound localisation in the auditory midbrain (David McAlpine, UCL Ear Institute).

The morning of day two was dedicated to cortical processing, and this included talks on the dynamics of population activity in the visual cortex (Matteo Carandini, UCL Institute of Ophthalmology), on pitch discrimination and sound localisation in the auditory cortex (Andrew King, University of Oxford), on understanding pain and pain relief through brain imaging (Irene Tracey, University of Oxford) and on the cortical processing of olfactory and taste stimuli (Edmund Rolls, Oxford Centre for Computational Neuroscience). In the afternoon, we moved on to central control of sensory processing; we heard talks on feedforward and feedback processes in visual grouping (Pieter Roelfsema, Netherlands Institute for Neuroscience, The Netherlands) and on descending control of spinal nociception (Bridget Lumb, University of Bristol). Regrettably, Mathew Diamond (SISSA, Trieste, Italy) was unable to deliver his talk since he had his wallet stolen upon his arrival in Britain and had to return home.

The last day was dedicated to motor integration and behaviour. Again, we heard fascinating presentations on a wide variety of subjects, including vomeronasal influences on behaviour (Peter Brennan, University of Bristol), action-based sensory coding in spinal sensorimotor modules (Jens Schouenberg, Lund University, Sweden), the contribution of single somatosensory cortex neurons to behaviour (Michael Brecht, Bernstein Center for Computational Neuroscience, Berlin) and feedforward and feedback learning in human sensorimotor control (David Franklin, University of Cambridge).

The first two days were concluded by lively round-table discussions in which participants were able to ask all sorts of questions they had not dared to ask earlier in the day. The roving mic proved essential for these sessions, which revealed a previously unknown talent of Maria Fitzgerald (UCL) as she metamorphosed into Graham Norton. These were followed by posters and trade exhibitions. In a close contest between many high-quality entries, The Society's Blue Riband poster competition was won by Annette Allen (University of Manchester), followed by Michael Bale (University of Manchester) and Laura Cornelissen (UCL). BCNC awarded a similar prize for the best oral communication by an early career scientist, and this was shared between Timothy Brown (University of Manchester) and Stephanie Koch (UCL) – it would be great if a similar incentive could be provided by The Physiological Society at future Themed Meetings.

The Society Dinner was held at Aberdare Hall, one of the first university halls of residence for women built in Britain. Entertainment was provided not only by band Capital Groove but also by Prem Kumar in his role as stand-up comedian aka Meetings Secretary. The meeting organisers thanked Sarah Barnsley and Nick Boross-Toby from The Physiological Society for all their hard work that contributed to making this meeting a very successful one. Thanks were also due to Vanessa Davies and Catherine Hortop from the Cardiff Neurosciences Centre and Anne Cooke from Bristol Neuroscience for their help with preparing the meeting.

The conference finished with a theme business meeting which provided an opportunity to alert Society Members to the deadlines for proposals for symposia at the 2011 Main Meeting as well as for the next Cellular & Integrative Neuroscience Themed Meeting, also to be held in 2011. Participants were reminded that the Themed Meetings are open to all Society Members with an interest in the respective theme, regardless of the perhaps narrower focus of invited talks on a particular topic. Please contact the Theme Leader, Frank Sengpiel (sengpielf@cf.ac.uk), with your ideas for proposals – the success of Cellular & Integrative Neuroscience as a theme depends on the active participation of all members!

Frank Sengpiel, Richard Apps and Bridget Lumb

An introductory workshop on human and clinical physiological techniques

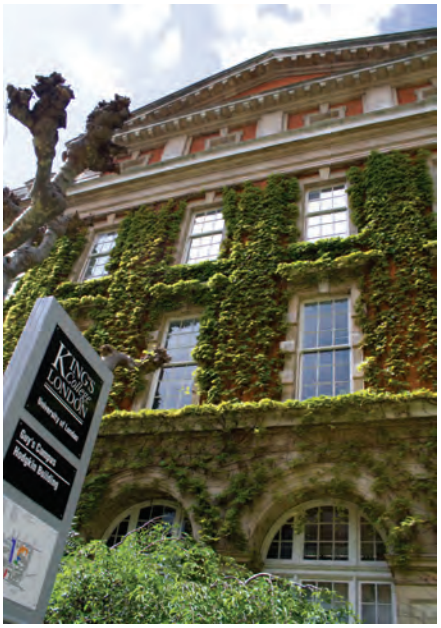
King's College and Imperial College London, 10 and 11 December 2009

From a PhD student's perspective: Stuart Goodall, Final year PhD student, Brunel University

London was chosen to be the venue for the first UK-based International Workshop on human and clinical physiological techniques. The two-day workshop at the beginning of December 2009 was held at King's College London and Imperial College London.

The workshop began with a series of lectures. Firstly, an insight into techniques used in human physiology was given followed by the human body response to high altitude. After brief refreshments, an intriguing lecture detailing acceleration physiology was presented and the response to cold water immersion followed. After lunch, delegates were given the opportunity to attend two of four practical sessions, covering a variety of applied techniques assessing human function. Practicals were led by experts in the relevant field; the small-group design provided a thorough understanding of the topic and we were free to ask questions at any time. To finish off the day, delegates were invited to participate in a poster session which served as a tremendous opportunity for us to network and discuss research.

The second day began with a choice of two practicals from four, all emphasising techniques that are used in a clinical setting. Mary Morrell and her research fellows ran practicals covering the areas of cerebral blood flow, EEG, application of non-invasive ventilation and measurement of chemosensitivity. As with the practicals on day one, we were in



small groups and they were hands-on, which provided a thorough learning experience. After lunch another series of informative lectures followed.

The workshop allowed me to meet students from all over the world and enhance my knowledge of physiological techniques. I am very appreciative of The Physiological Society for allowing the workshop to take place and also this year's organisers, Steve Harridge and Mary Morrell, who provided a thoroughly enjoyable programme.

From a research fellow's perspective: Dr Angela Atalla, Imperial College, London

There are some words every research fellow shudders to hear from their advisor. To the more conventional list, which includes enquiries about power calculations and ethics applications, I would suggest the addition of 'Would you like to give a lecture on respiratory loop gain to a group of international physiologists?'.

Our department was sent into a flurry of excitement at the prospect of hosting and organising a day of physiology workshops in December, as part of The Physiological Society's two-day International Workshop. Brainstorming and planning started in earnest back in the autumn and no member of the team was left out; workshops on non-invasive ventilation, chemosensitivity, EEG and transcranial Doppler occupied our waking hours as we prepared to play hosts to a varied mix of physiologists from all over the world.

As the week approached protocols were perfected, multiple choice questions concocted, and nerves ran amok. The more I prepared for my lecture on loop gain, the more the subject became an enigma to me and all chances of an erudite presentation seemed to slide away.

Daunted? We were. Apprehensive? Most certainly. Ready to rise to the challenge? Absolutely and completely.

The last few days saw an unprecedented level of activity in the labs and what was a veritable blitzkrieg spirit as the team pushed on to put the finishing touches to four workshops and various lectures. The work done we enjoyed meeting the attendees at an evening session where posters of previous work they had done were exhibited. As post-graduates, it's not often enough that we stray from the relative comfort of our own area of research so it was an unusual treat to be able to hear about such varied research topics from an enthusiastic group of people from such a wide variety of backgrounds.

Our day of hosting the workshop at Imperial College was a great experience for us all; we all learnt a lot about organising and hosting a large group, as we interacted with the attendees about our subjects. Perhaps the highlight for me was the final session given by two previous

PhD students who, having completed their PhDs in years gone by, came back to tantalise us with tales of their successes since graduating. An encouragement to us all. I was also gratified to hear that my lecture had gone down well and that people had understood my research area.

From an organiser's perspective. Dr Mary Morrell, Imperial College, London

You simply cannot organise an International Workshop without a great bunch of colleagues and the outstanding support of The Physiological Society staff. I was definitely blessed in this respect – everyone did a great job in producing a series of top-class sessions for the workshop, and the delegates did a great job in navigating their way across London from one campus to another, despite our directions!

We had been briefed that the delegates wanted hands-on experience, and this became our priority in organising the two days. The aim of the second day was to illustrate how different physiological techniques can be applied to research questions in a clinical context. This aim reflects my observations that communication between specialists can help to facilitate breakthroughs in clinical physiology, although it is a challenge to maintain the cross-theme communication if time is limited. The workshop was successful in that it attracted participants from many different countries and backgrounds. Indeed, it was both stimulating and encouraging to meet so many enthusiastic people from across the world. So as last cords of *Auld Lang Syne* fade away maybe we can look forward to a bright future for physiology in the new decade.

Microelectrode techniques for cell physiology

The Marine Biological Association, Plymouth, UK

8–22 September 2010

27th workshop

A variety of marine and other preparations will be used to illustrate the possibilities and limitations of these techniques. The workshop is intended mainly for postgraduate students and postdoc workers from any discipline who wish to learn techniques for use in their research.

Closing date for receipt of applications 30 April 2010

Application details from:
www.mba.ac.uk/microelectrodecourse.php
alexa@mba.ac.uk

Physiology in Simulation 2010 Bristol, UK

Hi-Fidelity Simulation Applied to the Biomedical Sciences

Physiology in Simulation 2010 is a workshop-based symposium aimed at presentation and discussion of developments in high-fidelity manikin-based simulation. The emphasis of the meeting is the application of physiological modelling to basic biomedical science and medical education.

Workshop & programme details to follow shortly

22/23 March 2010, University of Bristol

Organising committee- Dr Richard Helyer & Prof Judy Harris,
AIMS Centre for Excellence in Teaching & Learning, University of Bristol.
For further information contact- richard.helyer@bris.ac.uk +44 (0) 117 3311459

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Physiology in Simulation 2010 is organised, hosted and sponsored by the Applied and Integrated Medical Sciences (AIMS) Centre for Excellence in Teaching & Learning, University of Bristol, Bristol, UK

Hierarchical clustering of multidimensional data

Patricia de Winter

In the previous two articles of this series, we looked at how to go about finding which targets within a set of microarray data are statistically significant, taking into account the problem of multiple testing. At this point, we should therefore be armed with a list of significantly different genes, proteins, single nucleotide polymorphisms (SNP), or whichever other entity was the target (measured variable) of the array. For specialised applications that investigate a particular process, for example a microarray for cardiovascular-related genes, this list may not be too daunting, but in many cases arrays generate a list that can easily run into hundreds of targets, particularly when they are genome-wide studies for expression, DNA methylation or SNP. A lengthy enumeration of targets does not immediately reveal patterns in the data that can be visually summarised at a glance. This is in effect what hierarchical clustering can achieve.

Hierarchical clustering has become a popular way to summarise multidimensional data for a number of reasons: large data sets are readily simplified, groups of either targets or samples can be identified on the basis of similarity and the data are presented in the style of a phylogenetic tree, such as that used by taxonomists. Additionally, hierarchical tree diagrams or dendrograms are often combined with a heatmap, a matrix which allows individual values to be represented on a colour gradient, commonly from bright red through to bright green via black, with grey representing non-expressed or missing values (Fig. 1). In this figure, reproduced from *The Journal of Physiology*, each square represents the expression value in one sample for a given gene. In this figure, hierarchical clustering has been performed on 32 samples from human heart and Purkinje fibres and also on 79 ion channel genes so the matrix contains 32 x 79 squares (Gaborit *et al*. 2007). The dendrogram above the heatmap clusters samples into groups based on similarity of their ion channel gene expression: there are two major groups, or branches of the tree, one for atrial samples, and the other for ventricular and Purkinje fibre samples. The rightmost branch subdivides into two, separating ventricular samples from Purkinje fibre samples. The tree on the left-hand side of the heatmap clusters the ion channel genes based on their expression pattern across the samples, so for example, panel B genes are highly expressed in atria (mostly bright red), exhibit lower expression in the ventricles (mostly bright green) and moderately expressed in Purkinje fibres (black, dark red and dark green). In this analysis, the right and left atrial samples are indistinguishable from each another and similarly, left and right ventricular samples do not cluster separately. Deuteranopic males will experience some difficulty with this red–green visualisation so I will use an orange–blue gradient for heatmaps in the remainder of this article.

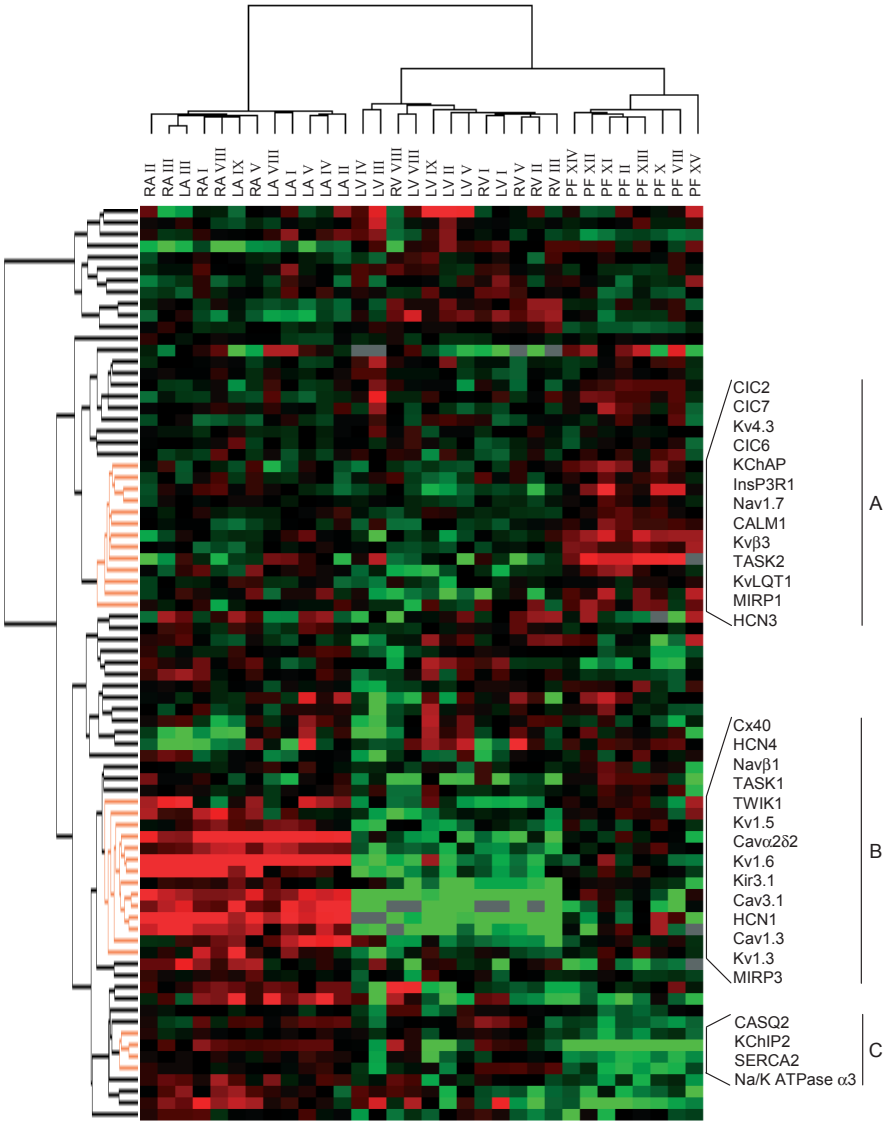


Figure 1. Example of hierarchical clustering of gene expression data. Reproduced from Gaborit *et al*. (2007), with authors' consent. See text for explanation.

Table 1. Illustrative data set derived from Gaborit *et al.* (2007). Samples are: LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; mean (±S.D.), $n = 7$.

gene	LA	LV	RA	RV
cav3.1	209.5 (131.50)	2.5 (0.1)	20.4 (8.3)	1.2 (0.8)
cavα2δ2	68.3 (82.0)	9.9 (5.1)	190.5 (101.2)	13.7 (5.9)
Kv1.5	690.6 (419.4)	31.8 (48.9)	652.8 (280.80)	26.3 (13.8)
Kv1.6	20.6 (8.2)	8.2 (8.0)	9.5 (2.0)	3.5 (1.9)
HCN1	270.9 (134.0)	5.4 (6.8)	71.8 (24.4)	0.4 (0.2)
TWIK1	687.5 (194.8)	128.1 (50.0)	759.1 (298.3)	210.3 (83.4)
TASK1	109.7 (37.2)	9.4 (6.6)	130.0 (84.2)	9.3 (6.2)
InsP3R1	140.8 (42.4)	127.9 (53.0)	116.9 (31.5)	152.6 (42.3)
CALM1	1471.3 (349.3)	1254.3 (274.1)	121.7 (30.5)	185.9 (19.4)
C1C2	7.9 (3.6)	7.2 (2.2)	10.5 (3.4)	12.7 (3.1)
Kv3.3	4.9 (1.1)	3.3 (0.6)	2.9 (0.5)	1.7 (0.5)
Kvβ2	119.5 (21.6)	240.9 (72.4)	23.4 (3.5)	46.4 (4.7)
KIR3.1	327.9 (30.8)	7.1 (3.0)	159.5 (22.1)	3.8 (1.3)

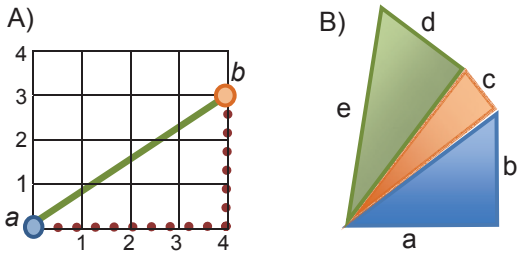
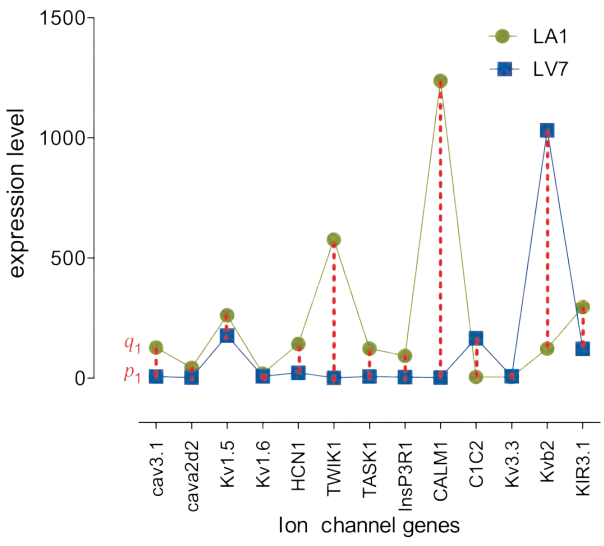


Figure 2. A, Euclidean and Manhattan distances plotted on Cartesian co-ordinates. The Euclidean distance of two points a and b (blue and orange circles) is represented by a continuous green line and can be calculated using Pythagoras' theorem. The Manhattan distance is represented by the dotted lines. B, Pythagoras' theorem can be extended to any number of dimensions, here $a^2 + b^2 + c^2 + d^2 = e^2$.

In this article, to simplify explanations and the somewhat large dataset, I will omit the Purkinje fibre samples and use a small selection of ion channel genes from Gaborit *et al.*'s paper. I have selected 13 ion channel genes from the supplemental information file and for each gene have generated four random sets of data that have a mean and standard deviation similar to that of the original (Table 1).

Distance measures

We will now examine the dendrogram in more detail. The nodes (intersection of horizontal and vertical lines) can be rotated without affecting the information, that is the dendrogram exhibits isomorphism and can be drawn in many ways. The length of the branches is proportional to the distance of one profile to another: profile here is defined as either a data column (sample profile) or a data row (gene profile). Distance is a measure of similarity between profiles and can be calculated in a number of ways, the commonest of which are Euclidean, Manhattan and correlation. Euclidean and Manhattan are geometric measures of distance that in two-dimensional space can be plotted using Cartesian co-ordinates (Fig. 2A). The Euclidean distance, d, between the two points, a and b, can be obtained by using Pythagoras' theorem (eqn (1A)): $\sqrt{(4^2 + 3^2)} = 5$. The Manhattan (also known as city block) distance for this point would be the sum of the dotted lines, or 7. Euclidean and Manhattan distances generally produce similar clusters, but from the Manhattan distance the effect of large values or outliers is lessened as the calculation does not include a squared term. We will look at Euclidean distance in a little more detail. Pythagoras' theorem can be extended from triangles to any shape (Fig. 2B), or indeed anything that can be represented by numbers in order to calculate Euclidean distances between sets of data. For microarray data, the Euclidean distance, d, between two sets of numbers P and Q, in this case two profiles, can be given by



Equation 1A. $$d(a,b) = \sqrt{(a_1 - b_1)^2 + (a_2 - b_2)^2}$$

Equation 1B. $$d(P,Q) = \sqrt{\sum_{i=1}^{n} (p_i - q_i)^2}$$

Equation 1C. $$d(P,Q) = \sqrt{\sum_{i=1}^{n} |p_i - q_i|}$$

Figure 3. Eucidean and Manhattan distances applied to multidimensional data. The Euclidean distance between two profiles, in this case an atrial and a ventricular sample (LA1 and LV7, respectively), can be calculated using eqn (2B). The vertical dashed red lines represent the difference in expression for each gene on the abscissa, or $p_1 - q_1$, which are then squared and summed. The square root of this value is the Euclidean distance. The Manhattan distance is simply the sum of the differences $p_1 - q_1$.

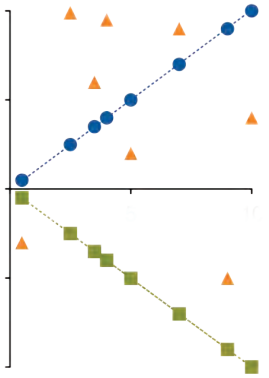


Figure 4. Scattergram illustrating correlation – perfectly positively correlated variables (blue circles), perfectly negatively correlated variables (green squares) and uncorrelated variables (orange triangles). Pearson's correlation coefficient = 1, –1 and –0.14, respectively.

Pythagoras' theorem (eqn (1A)) applied to multidimensional data (eqn (1B)). If the squared term is removed from eqn (1B), and the term $p_1 - q_1$ is bracketed by a modulus (absolute values) this gives the Manhattan distance (eqn (1C)). Although Euclidean distance for such data cannot be represented directly on a graph, I have attempted a visual representation using a pair of sample profiles recreated from Gaborit *et al.*'s data (Fig. 3). These data are in fact profiles generated from quantitative PCR rather than hybridisation to microarrays, but the data are analysed in the same way. In this example I have compared two sample profiles, but as with any of these measures of distance, the same analysis can be applied to gene profiles. A disadvantage of these geometric measures of distance is that they are not scale invariant; two profiles that exhibit a similar *pattern* of expression, but vary greatly in *magnitude*, will appear very distant.

Correlation is a measure of distance that is computed by a statistical test. If two identical profiles are plotted, all the data points will fall on a straight line with no scatter, and if the data are subjected to a correlation analysis, Pearson's correlation coefficient, *r*, will be unity (Fig. 4). The distance, *d*, between these profiles is computed as 1 – *r* and is therefore zero. The smaller the value of *r*, the greater the distance between profiles, to a maximum distance of 1. A negative value for *r* means that two profiles are inversely correlated; for example, downregulation of one gene is accompanied by upregulation of another. For a perfectly negative correlation *r* = –1 and the two profiles will also have a distance of zero between them – the negative value of *r* is squared prior to subtracting from 1, so that distance remains a value between 0 and 1. A well-known disadvantage of Pearson's correlation method is that it is very sensitive to outliers: a single data point can produce a correlation where there is none, and outliers are not uncommon in microarray data. For this reason, it is more common to use Spearman's correlation for microarray data. In Spearman's correlation, the data are replaced by ranks, which greatly reduce the effect of outliers. One disadvantage of Spearman's correlation is that the direction of change in gene expression is lost during the ranking process. It is worth noting that correlation in this context is not being used to test a null hypothesis of no correlation between groups of samples or genes; hierarchical clustering is not an inferential statistical method.

Making profiles comparable

Prior to applying a measure of distance it is common to adjust the data to make profiles comparable. I deliberately avoid the use of specific terms here because every book, software manual or web page I have read uses the same term for different mathematical procedures. Before adjusting your data, it is essential to read the manual for the data analysis software you are using to determine how a particular procedure will affect it. The commonest procedure is to subtract the mean value of a profile from each observation in that profile, and then to divide the profile standard deviation into each calculated difference. The

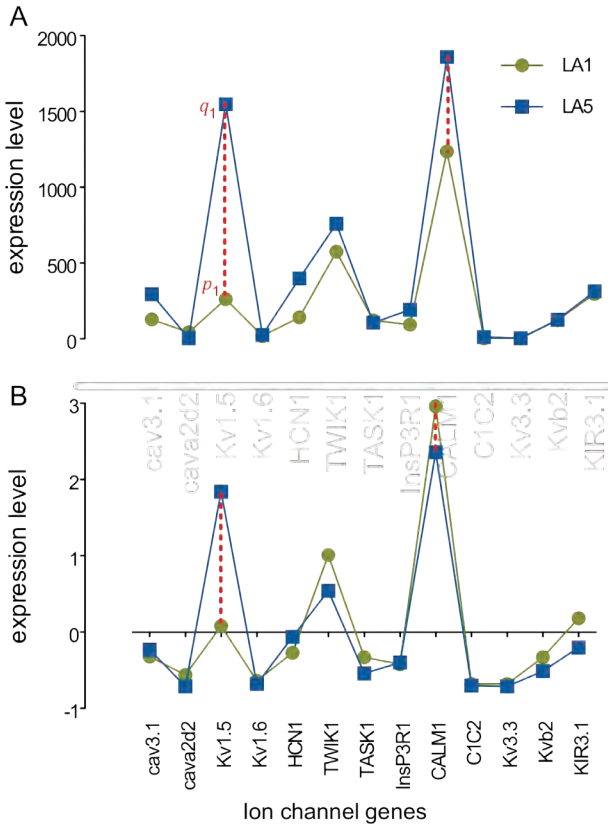


Figure 5. The profiles of two left atrium samples are plotted without adjusting the data (A) and after rescaling so that the mean of each profile is equal to zero with a standard deviation of 1 (B). Note that in B, the dotted red lines $p_1 - q_1$ are shorter overall (for clarity, only the longest two are shown in each graph) so both Euclidean and Manhattan distances decrease. The pattern of expression remains similar following adjustment.

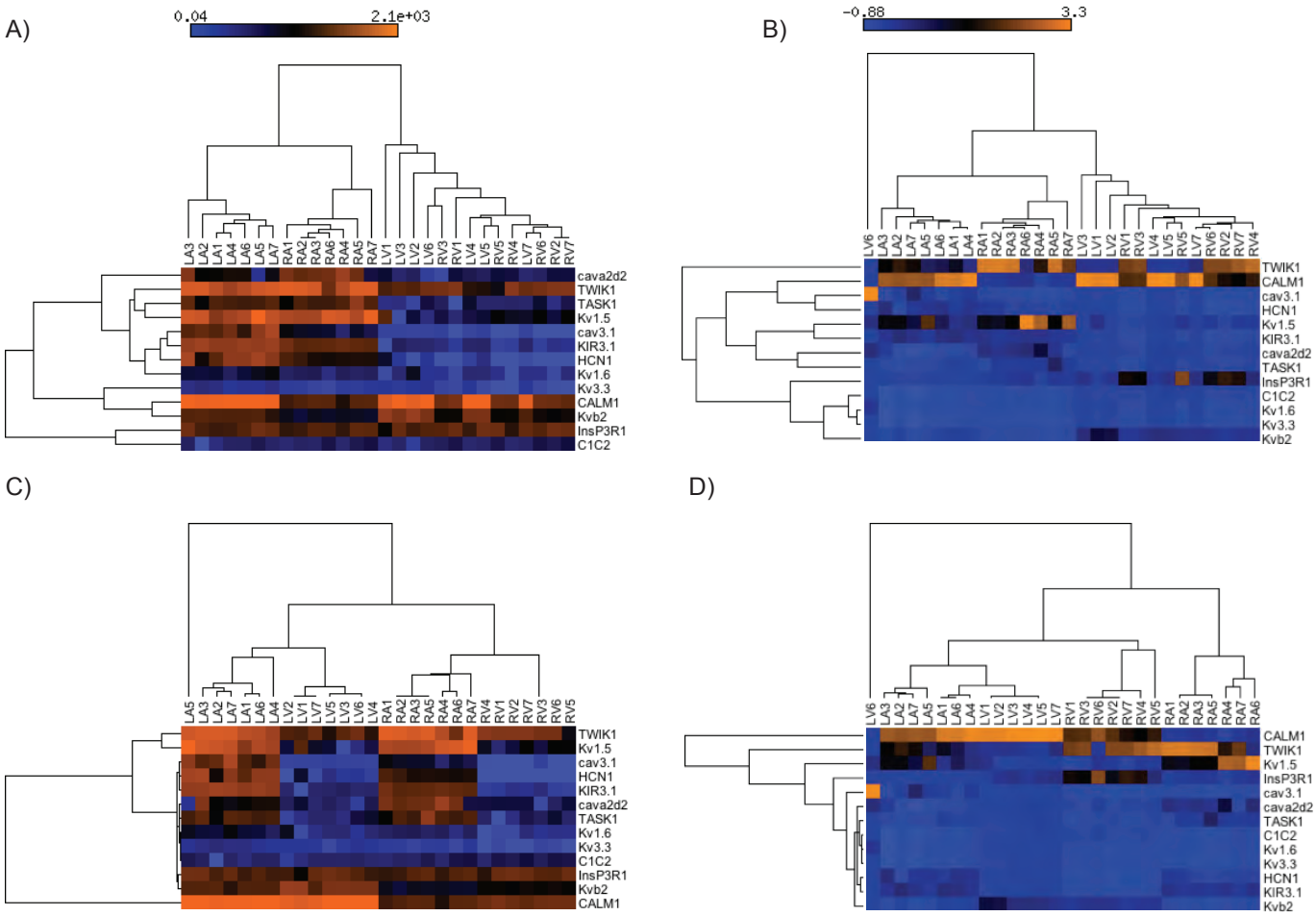


Figure 6. Unsupervised hierarchical clustering of randomly generated datasets derived from Gaborit *et al*. (2007). Group means ± S.D. are reported in Table 1. Spearman's correlation (A and B) or Euclidean distance (C and D) were performed on unadjusted data (A and C) or following adjustment so that profiles have a mean of zero and standard deviation of 1 (B and D). For the sample dendrogram (clustering of column data), right atrial samples consistently cluster into one group, irrespective of the method used. Clustering of left atrial and ventricular samples exhibits dependence upon the method; however, with the exception of sample LV6, correlation is able to distinguish atrial and ventricular samples. For the gene dendrogram (clustering of row data), clustering exhibits strong dependence upon the method.

mean of this new data set will be zero with a standard deviation of 1. This procedure standardises the data to z-scores and is applied to all profiles. The effect of this procedure on geometric distances of profile data is illustrated in Fig. 5. For geometric distances, this overcomes the problem of sensitivity to scale, discussed above. For Pearson's correlation where the samples are not a time series, this simplifies the calculation of *r* and is recommended; however, when the data are a time series, the direction of change in gene expression may be lost.

Linkage methods – building the dendrogram

In order to compute distances between profiles for clustering and start building a dendrogram, all possible pairs of profiles are compared with each other to find the pair that has the smallest difference between them. This would be laborious by hand but is computed in milliseconds by clustering software. When both row and column data are subjected to clustering this is known as unsupervised hierarchical clustering. If, for example, we wish to cluster genes but keep the samples in some order that we impose, such as treatment groups, the clustering is supervised. The samples in Fig. 1 were clustered using correlation and the two that were most closely correlated were RAIII and LAIII, so this cluster pair has the shortest branches. In order to find the distance between a cluster and remaining profiles, a method called linkage is used. For microarray data, the commonest method is average linkage. The mean of each pair of observations (measurements) for the two most similar profiles is calculated to produce a new 'average' profile, and the distances between this cluster and all other profiles is recalculated to find the profile or profile pair nearest to the averaged profile. The process is repeated until the tree is complete. As profiles and clusters are added, the tree's branches lengthen because the distances become larger. An alternative linkage method that is also used for microarray data is complete linkage. Rather than averaging profiles, the observations in the first cluster (that with smallest distance value) are compared with those in all the other profiles to find the two observations that have

the largest difference between them. Only the profile in the first cluster that contains one of the two observations is used to recalculate the distances between the remaining unclustered profiles to find the next nearest profile or cluster, and so forth. The opposite of this is to use the smallest rather than largest observed differences and is called single linkage, but as this tends to produce an effect called 'chaining', where the tree lacks fine detail, it is not usually used for microarray data. Complete linkage generally produces compact, well-defined clusters and works well where there are strong patterns in the data. It does not perform as well when the data are noisy, as microarray data often are. Average linkage is an intermediate between single and complete linkage and tends to perform well with microarray data.

The reliability of hierarchical clustering

It should now be evident that the choice of distance measure and linkage method can have a profound effect on the outcome of hierarchical clustering. This is illustrated by the differences between the four dendrograms in Fig. 6. The reliability of hierarchical clustering can be assessed objectively. A permuation test can be applied to determine whether the clustering differs from that which would occur by chance alone. I gave a detailed explanation of permutation tests in the first article of this series and thus it will not be repeated here [2]. The advantage of this method is that it returns an exact probability and is free from subjectivity.

In the next article of this series, principal component analysis will be explored.

Patricia de Winter

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Letter from America – To study motion, how closely must you live with it?

Having bookended extensive time 'on the road' with studies into human movement, I have mirrored my work in the lab with a life filled with motion. Travel has long been described as a function for a state of peace and knowledge, but just as Kurtz in Conrad's *Heart of Darkness* is driven mad by the environment and his distance from 'home', how would I fare with movement research, while on the road?

Over the past two years, I have had the pleasure of roaming through India, living in Australia, climbing volcanoes in Guatemala, sun baking in Mexico, snorkelling in Belize and finally living in New York. I began my journey studying and writing my Honours thesis on the neurophysiology of movement, and ended it working in motor control at Columbia University in New York. To my knowledge, I have escaped Kurtz's fate and my movements and travels have clarified my ideas and thoughts on my studies.

After my degree in my hometown of Sydney, Australia, I was lucky to take an optional year of research at the Prince of Wales Medical Research Institute, supervised by Richard Fitzpatrick. This meant my previously purely academic studies were supplemented with 'home mechanics' forays into welding, wood construction, circuit design, beginner's programming and How To Use Bicycle Parts To Create A Terrifying Apparatus 101. I became very good at diverting the attention of subjects from the steel-, cog- and bolt-ridden planks upon which I conducted my experiments. To study our perception of ground height as we walk, I measured healthy subjects' limits of height detection between their feet – their height threshold – by making them stand or walk over increasingly smaller changes in height. The year was an intense one but I enjoyed it and moved along a very steep learning curve about physiology research.

My best friend, Bonnie, and I (left) enjoying the ambient static electricity on top of a Guatemalan volcano. Two minutes later lightning struck!

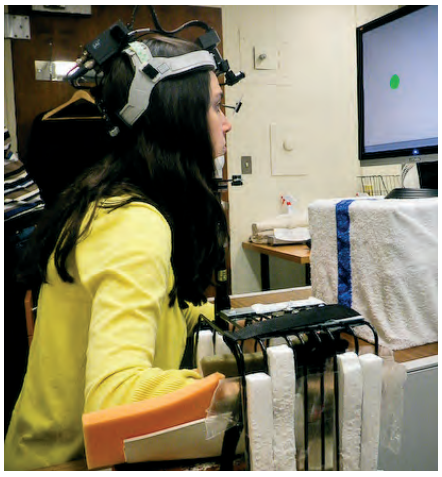
By the time I had finished writing up my thesis and presenting it in November of 2008, my feet were itching. During the year my interest in studying medicine had grown but the year-long application process looked, well, long. I had left for India by 1st December. Watching snake charmers and intricate Indian dances fed my interest in neuromotor research, while days suffering with bouts of 'Delhi belly' fuelled my desire to go to medical school. By the time I returned to Australia, I sent in my application and decided to spend the year living in New York City with my best friend to stretch myself both professionally and academically. Or at least that's what I told my parents. With friends, we diverted through Central America for 2 months.

In perhaps the only instance of a Canadian citizen flattering the USA, Sir Francis Head wrote, 'the heavens of America appear infinitely higher – the sky is bluer – the air is fresher – the cold is intenser – the moon looks larger – the stars are brighter – …' He goes on. This was when the USA was described as 'the new world', and needless to say, things have changed. My first contact with the States was in the suburbs of Anaheim, California, where not much can be described as 'fresh' except for the layer of paint on the Disneyland rides, and plenty of things are 'large', but the moon would be the last thing on my list.

On arriving in New York, I was eager to investigate the American style of

research and took an opportunity to meet and work with Pietro Mazzoni, co-director, with John Krakauer, of the Motor Performance Lab in the Department of Neurology at Columbia University, in uptown Manhattan. The experience of moving to a new city, finding a place to live, learning my way around and trying to avoid being run over was an overwhelming one. I expected to be similarly out of my depth when I met with Pietro and the lab at Columbia. I was, but in a different sense. The research being done at the Motor Performance Lab was incredible – it had the uncommon combination of being both clinically applicable and theoretically profound. As a 22-year-old from Australia, fresh out of my Bachelors degree, there were many 'little fish, big pond' moments. Despite this, learning about the lab made me feel much more comfortable than many of the other cultural lessons I had been discovering. Science research is arguably the most international of professions; pushing back the boundaries of knowledge requires sharing results and ideas. There was constancy to equipment, the techniques and the attitudes that made me feel a comfort that I'm sure many other researchers have found in a lab in a foreign city.
My work at Columbia University centred on a trade-off that exists in the motor system between speed and accuracy, called Fitts' Law. This describes a robust inverse logarithmic relationship between the speed of a movement and its necessary accuracy. Of particular interest was how submovements – the hypothesized simple components of gross movement – optimized the speed–accuracy trade-off.

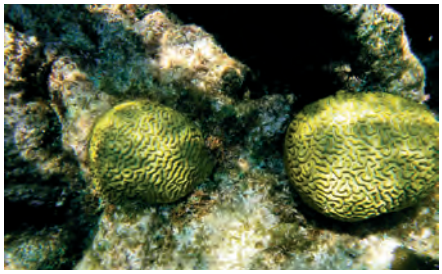
Meanwhile, life in New York started to feel more natural. I travelled back to Australia for my medical school interview and had the usual traveller's realisation that nothing much seems to have changed when you return. A highlight of the latter part of the year was attending the Society for Neuroscience Chicago conference. It was only the second conference I had ever attended



A fellow researcher, Sophie Ryan, demonstrating the motor study setup at Columbia University.

(the first was the 2009 Australian Neuroscience Society conference at which I presented a poster) so to say it was the largest is not a powerful statement. Nonetheless, nearly 31 000 neuroscientists descending on the Chicago convention centre is quite a sight!

As I write this in my final days at the Motor Performance Lab, I am excited to return home and start medical school, but am also filled with a sense of unfinished business. It seems that the more experiments you do, the more you discover you need to find out. I have spent the past two years moving through parallel experiences: treading across several countries with only a growing list of all the other places I must explore, and roaming around the realm of the neuromotor system asking more questions than I could ever have answered.



Brain coral in the Caribbean.

As Saint Augustine was reputed to have said, *solvitur ambulando* (it is solved by walking). I hope to keep travelling and return to physiology research soon, and with more ideas.

Joanna Offord

Measurement of gene expression using real-time quantitative PCR

29–30 March 2010, King's College London

The Physiological Society is sponsoring a 2-day 'hands-on' workshop to learn the principles of qPCR, focusing on the practical steps required to design, set-up, validate and analyse real-time qPCR assays.

Enquiries and registration: education@physoc.org

Course organised by David Sugden and Patricia de Winter

Meetings accommodation

Student accommodation has improved immeasurably in the 50-odd years since I started attending Society Meetings. I have memories of some very peculiar rooms, some so peculiar that it is best not to identify any of them. There was the high building in a gale-prone city that swayed so much it gave a nautical quality to ones sleep. In another residential block, the lifts served every other floor – specifically the floors that didn't have bathrooms. A particular challenge was mounted by the safety-minded university where overloading of electric circuits was prevented by a trip switch in the corridor outside each room. People arriving in the evening gloom could just about read the notice explaining how to reset the trip. Later arrivals went to bed in the dark and grumped all through breakfast.

Ann Silver

Leptin receptor regulation – links to obesity?

Obesity is characterised by high circulating levels of leptin, a hormone that limits the amount of body fat. This paradox has led to the concept of leptin insensitivity in obesity. We investigated the regulation of leptin receptor gene expression and protein number in response to leptin and diet to see whether receptor regulation could play a role in the development of leptin insensitivity

Leptin was first discovered when the obesity seen in the *ob*/*ob* mutant mouse was identified as being due to a single gene mutation resulting in the complete lack of the hormone leptin. Similar mutations, although very rare, have been found in humans, with leptin replacement reversing obesity, emphasising the role of leptin in the maintenance of a lean body mass.

Leptin is mainly produced by fat. Leptin can act as a long-term signal to the brain that adequate energy is stored, and can also act as a short-term signal, with levels dropping during fasting. Leptin receptors are present in many tissues. The key site of action for leptin is in the brain, particularly the 'energy balance centres' in the hypothalamus. Normally, leptin signals the hypothalamus to inhibit feeding and increase energy expenditure, thereby maintaining 'normal body weight'. However, high levels of circulating leptin, which occur in obesity, fail to stop overconsumption, leading to the concept that in obesity the loss of potency of leptin is due to leptin 'insensitivity'. A number of different mechanisms have been proposed to account for the development of leptin insensitivity. It has been suggested that leptin receptor signalling may be impaired, for example, by high levels of suppressor of cytokine signalling 3 (SOCS3), an inhibitor of leptin signalling via the Janus kinase 2 (JAK2)/ signal transducer and activator of transcription 3 (STAT3) JAK/STAT pathway. Signalling is terminated in part by the induction of SOCS3 production. The induction of SOCS3 gene expression can be used as a marker of induction of the JAK/STAT pathway.

The potency of hormones is regulated in part via the presence

Lynda Williams and Ruben Nogueiras

of specific receptors. Five isoforms of the leptin receptor have been identified to date; Ob-R(a–e). However, only the long form of the receptor, Ob-Rb, is capable of eliciting a full signalling response. The short forms of the receptor, Ob-Ra and Ob-Rc, are thought to act as leptin transporters into the brain as they are present on the choroid plexus and on the brain microvessels.

We set out to look more closely at the regulation of leptin receptors in the brain, in particular the short forms on the choroid plexus and the long form on hypothalamic neurons, to find out more about how gene expression and/or receptor number were changed by circulating levels of leptin, diet and nutritional status (Mitchell *et al*. 2009). We used *in situ* hybridisation for gene expression studies and *in vitro* autoradiography to visualise labelling the receptor with the ligand [^{125}I]leptin. These are

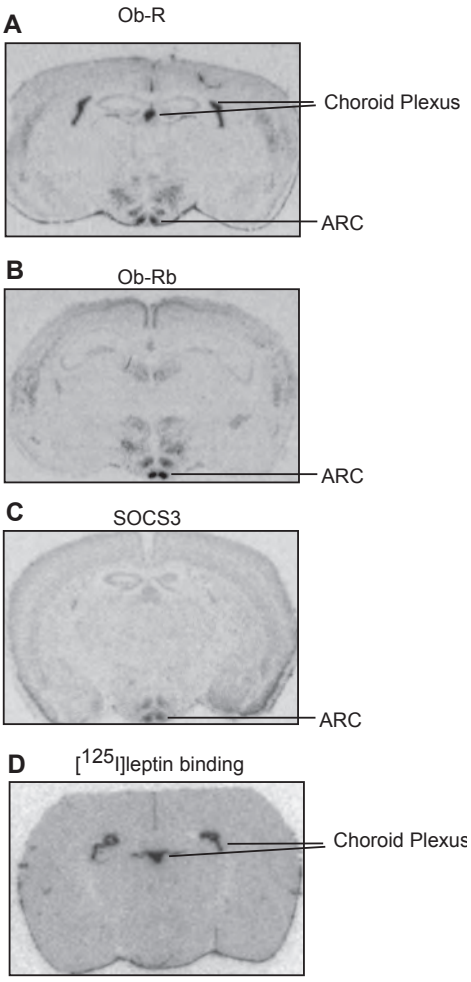


Figure 1. *A*, the distribution of leptin receptor gene expression. Ob-R – all forms of the receptor and *B*, Ob-Rb – the long signalling form of the receptor. *C*, SOCS3 gene expression and *D*, [^{125}I]leptin binding in sections of mouse brain.

ideal techniques for looking at gene expression and receptor number in complex tissues such as the brain as the signal over each anatomically distinct area can be quantified separately (Fig. 1*A–D*). We wanted to know what factors regulate leptin receptor gene expression and number, and whether receptor regulation could play a role in the development of leptin insensitivity.

We looked at receptor gene expression and receptor number in the brain of the C57Bl/6 mouse by manipulating the level of leptin by fasting, which drops leptin levels, refeeding, which raises leptin levels back to normal, and feeding a high-fat diet, which raises leptin levels in response to increased adiposity. We also injected leptin to further raise levels, in normal mice and those on a high-fat diet, to see if a high-fat diet would interact with the effect of leptin on the regulation of receptor gene expression or number.

A drop in the level of circulating leptin, seen in fasting, gives rise to increases in both receptor number and receptor gene expression in all regions of the brain measured. The fasting-induced drop in leptin appeared to be important for the subsequent down-regulation of gene expression and receptor number in response to increased leptin levels seen on refeeding. This was emphasised by the fact that increasing the levels of circulating leptin by both a high-fat diet and by injecting leptin had more complex effects on gene expression and receptor number depending on the region of the brain examined and on whether the long or short forms of the receptor were measured.

We were able to identify two potential mechanisms by which obesity may induce leptin insensitivity via receptor regulation. The first was the down-regulation of receptor number by high levels of circulating leptin (Fig. 2*A*). Data from studies in cells transfected with a green fluorescent protein (GFP)-tagged leptin receptor from our lab and others (Belouzard *et al.* 2004) shows that the endocytosis of the receptor into the cell is constitutive and that leptin has no influence over the rate of uptake into the cell. This indicates that down-regulation of receptor number at the cell surface must be the result of intracellular retention of the receptor. Leptin receptors are mainly localised to the Golgi and trans-Golgi network (TGN) in the cell (Fig. 2*B*). However, both smaller increases in the level of leptin induced by high-fat feeding and decreases in leptin levels during fasting, resulted in an increase in receptor number on the choroid plexus. High-fat feeding and fasting have been shown previously to down-regulate the transport of leptin into the brain (Kastin & Akerstrom, 2000; Banks *et al.* 2004). One explanation for this counter-intuitive increase in receptor number may be that normal transport of leptin through the cell via the receptor is inhibited by high-fat feeding, which leads to an increase in the number of receptors trapped at the cell surface.

Another mechanism by which obesity may cause leptin insensitivity is the inhibition of the up-regulation of the expression of the long signalling form of the receptor by leptin (Fig. 3*A*). The up-regulation of the receptor by leptin was unexpected as some reports have found that a down-regulation of the receptor occurs in obesity but other studies have found no

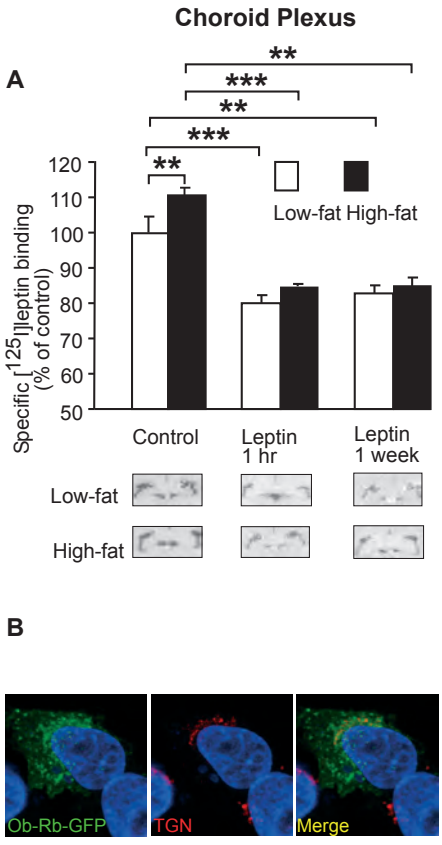


Figure 2. *A*, changes in the level of [^{125}I]leptin binding in response to high-fat diet and leptin challenge. *B*, the long form of the leptin receptor coupled to green fluorescent protein (Ob-Rb-GFP) expressed in CHO cells colocalises with trans-Golgi network (TGN) specific inmmunoreactivity.

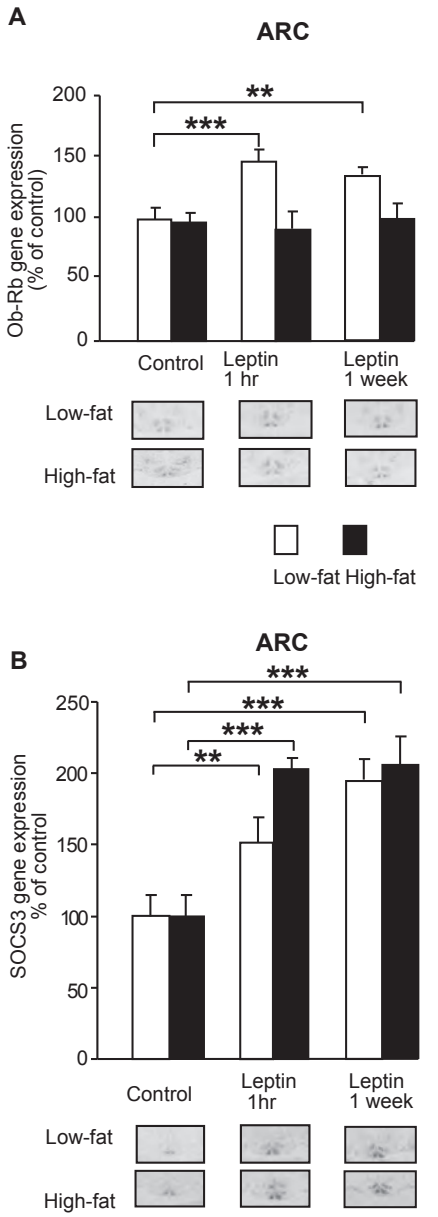


Figure 3. *A*, the effect of high-fat diet and leptin challenge on the level of Ob-Rb; *B*, SOCS3 gene expression in the arcuate nuclei (ARC) of the hypothalamus.

down-regulation. The increase in receptor gene expression seen in the present study is prevented by the high-fat diet but is not associated with the inhibition of leptin signalling via the JAK/STAT pathway as the induction of SOCS3 is not inhibited (Fig. 3*B*). This indicates that one of the other leptin signalling pathways may be important in this response – but this remains to be tested.

Our study points to the fact that the leptin receptor has evolved to be regulated by low circulating levels of leptin, whereas high circulating levels of leptin and a high-fat diet may interfere with normal regulation of gene expression and receptor number.

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Does activity in the lateral cerebellum reflect predictive control of visually guided movements?

How do we track a moving target accurately with our eye or hand? In order to overcome the long neural delay in processing visual feedback information, it is necessary to predict the future position and trajectory of the target if it is to be tracked with accuracy. Predictive behaviour can be achieved through internal models, and one structure that has been implicated as a key site for their operation is the cerebellum

For activities as diverse as catching a ball, or reaching out to pick up a cup of coffee, the cerebellum is thought to play a prominent role in the accurate execution of visually guided movements. But how exactly the cerebellum controls the interactions between our limbs and the external environment is a matter of debate. Behavioural experiments have shown that the minimum interval needed for visual information to influence an ongoing movement is approximately 80–100 ms. This neural delay time in sensory processing and motor execution is far too long to permit effective feedback control; therefore, one must be able to predict and anticipate the position and trajectory of the target. One structure that seems particularly critical in this prediction process is the cerebellum.

Nadia Cerminara

Predictive behaviour can be achieved through internal models (Miall *et al.* 1993; Wolpert *et al.* 1995). Broadly speaking, internal models are defined as neural representations of our bodies and objects in the external environment and can be of two types: forward and inverse. Forward models make predictions about the behaviour of the motor system and external objects whereas inverse models transform a desired goal into the appropriate plan of action. The cerebellum is thought to form internal models through a learning process in which a simulation of the desired movement is constructed and modified by repeated practice of the movement. This allows us to rapidly and precisely execute a desired movement without depending exclusively on on-line sensory feedback from the moving body part to guide the movement.

In the context of moving our limb towards an object, say a cup of coffee, a forward model would predict the position or velocity of the limb, whereas an inverse model would transform the desired trajectory of the limb into the appropriate joint forces/torques. However, there is disagreement in the literature regarding the existence of inverse *versus* forward models in the cerebellum. On the one hand, Purkinje cell activity in regions of the cerebellum concerned with eye movements have been interpreted as representing inverse models (Gomi *et al.* 1998). On the other hand, in a recent study of non-human primates performing a circular manual tracking task under various force loads, Purkinje cell activity was not altered with the change in hand force and arm muscle activity that occurred as a result of varying the loads (Pasalar *et al.* 2006), leading to the conclusion that rather than an inverse dynamics model of the arm, Purkinje cell activity represents the kinematic output of arm movements. This kinematic representation may in fact correspond to the output of

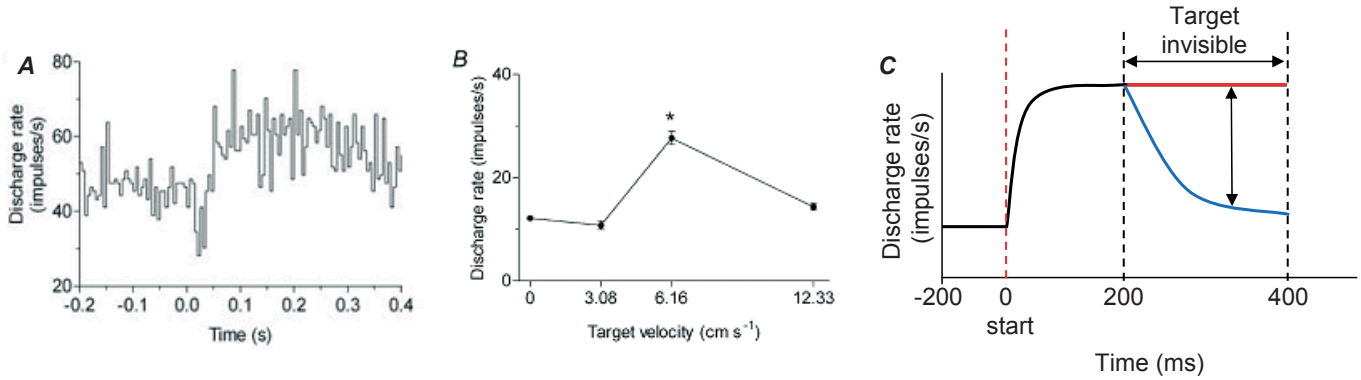

Figure 1. *A*, representative example of a Purkinje cell that showed tonic activity during target motion. The onset of target motion occurred at time point 0. *B*, example of a Purkinje cell that showed significant modulation ($P < 0.05$, one-way ANOVA, $n = 7$) to a 'preferred' target velocity of 6.2 cm s^{-1}. Each data point represents mean tonic discharge rate ± S.E.M. *C*, schematic diagram demonstrating the expected Purkinje cell activity if tonic activity that would occur when visibility of the target was occluded, if activity simply reflects actual target motion driven by the visual stimulus (blue line) or if activity is due to the construction of a forward model of its motion (red line). (Adapted from Miles *et al.* 2006.)

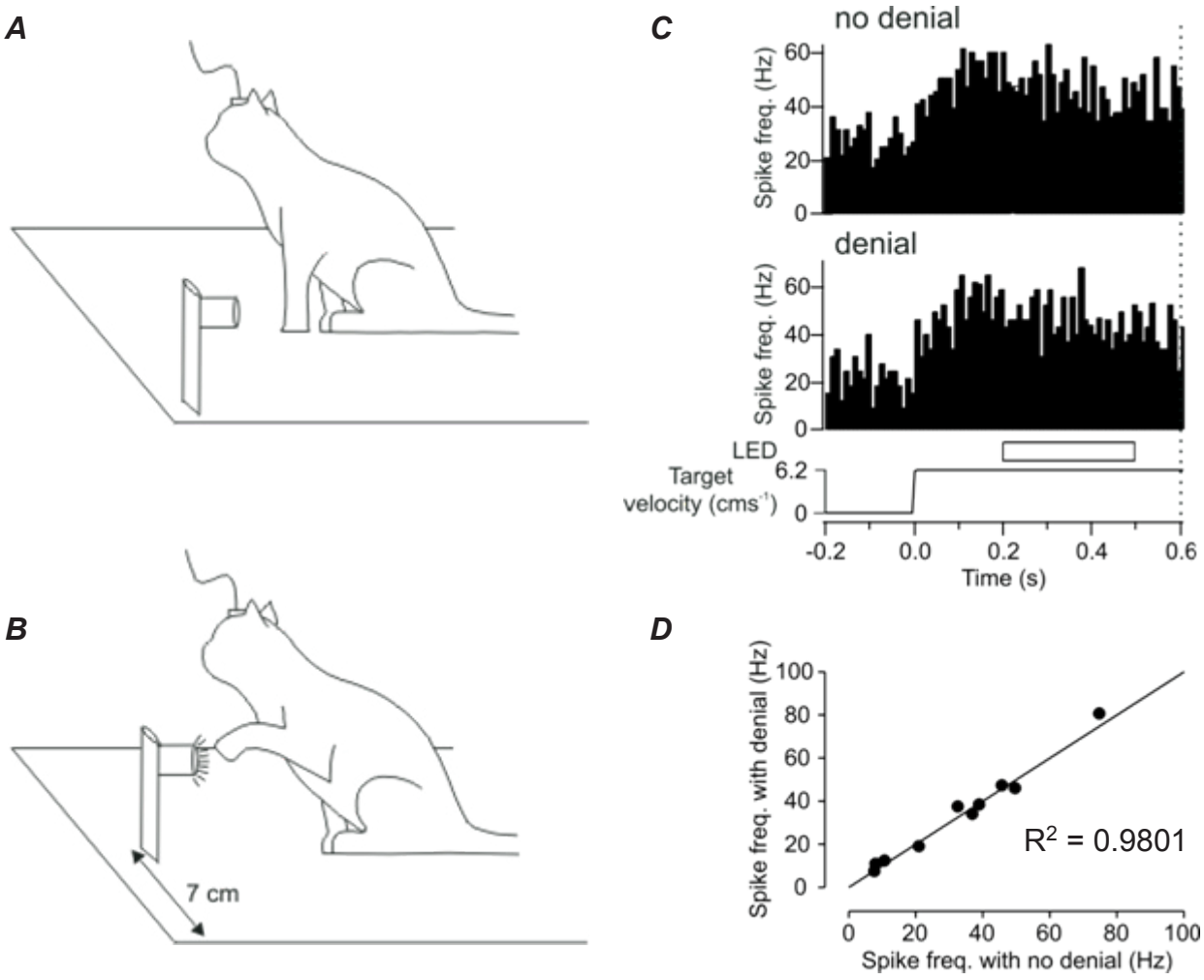

Figure. 2. *A* and *B*, schematic diagram of behavioural task. Cats were trained to perform a visually guided reaching task in the dark in which a tube, dimly lit by a ring of LEDs and containing a food reward, was initially stationary 7 cm to the left of centre. *B*, in a 'go' trial, the tube started to move horizontally in the rightwards direction at a constant velocity of 6.2 cm s^{-1}. After an interval of approximately 600 ms after the commencement of target motion, the LEDs brightened to cue the animal to make a reach with its left forelimb, ipsilateral to the cerebellar recording, to retrieve a food reward from the tube. *C*, peri-event time histogram (PETH) showing an example Purkinje cell which displayed a tonic increase in simple spike activity in relation to target motion. In one half of the trials, the moving target disappeared for 300 ms during target motion. Target denial occurred 200 ms after the onset of target motion. Dotted vertical line at 0.6 s represents 'go' signal. *D*, comparison of responses during target denial with no denial control. No significant change (paired *t* test, $P > 0.05$, $n = 10$). Line represents unity. (Adapted from Cerminara *et al.* 2009.)

a forward model that predicts the consequences of limb movements. Therefore, in relation to control of parts of the body, such as the eyes or limbs, the debate between forward and inverse models remains unresolved.

One way to inform the debate is to seek evidence for the existence of internal models in the cerebellum of the movement of objects in the external world. The situation here is simpler; if an internal model of an external moving object exists, it can only be of the forward type, making predictions about the object's future position and velocity. When pursuing a moving target, it is necessary to overcome the delays in visual feedback by predicting the future location of the target based on its motion. It has been suggested that on-line visual information is combined with a representation of target kinematics to make an internal model and hence predict future target location (Barborica & Ferrera, 2003). Indirect evidence for the operation of internal models in the lateral cerebellum of objects and tools in the external world has been obtained in human imaging studies (Imamizu *et al.* 2000). However, to obtain direct evidence recordings from individual cerebellar neurones are required.

Previous work from our laboratory (Miles *et al*. 2006) in cats trained to perform a visually guided reach–retrieval task has shown that Purkinje cells in the lateral cerebellum, a region known to be involved in the visual guidance of movement (Stein & Glickstein, 1992), were responsive to the on-going motion of the visual target, displaying tonically altered rates of simple spike discharge for as long as the target was moving (Fig. 1*A*). The altered tonic discharge rate was found to encode the speed of the target, as individual Purkinje cells displayed a 'preferred' target velocity when tested against a range of speeds (Fig. 1*B*). Since the cats were familiar with the motion of the external target which moved in a predictable fashion, could this pattern of neural activity reflect the operation of a forward model? Alternatively, was the neuronal activity simply coding the on-line motion of the target driven by the visual stimulus?

In order to distinguish between these two possibilities, temporary visual denial of the target can be used. Whilst invisible, the tonic increase in discharge rate usually seen whilst the visible target is moving would be expected to disappear if the cells were being passively driven by the sensory stimulus whereas such activity would be expected to survive if a forward model of target motion had been formed (Fig. 1*C*).

Again we used single unit recordings in cats trained to perform a predictable visually guided reaching task. Cats were trained to reach (after receipt of a 'go' signal) into a moving visual target travelling horizontally at a constant velocity. The target for reach consisted of a hollow Perspex tube dimly lit by a ring of LEDs. The tube was initially stationary 7 cm to the left of centre (as viewed by the cat) at a comfortable height for reaching (Fig. 2*A*). The tube then moved at a constant velocity rightwards across the cat's visual field (Fig. 2*B*). Experiments were conducted without ambient illumination in a light-proof room. Thus, the only source of visual information available to the cat was from the target LEDs. At various stages of the target's motion, illumination of the ring of LEDs around the tube was temporarily extinguished during which time the animal was in total darkness.

For target-related Purkinje cells that displayed tonically altered simple spike activity during on-going movement of the visual target, there was a similar pattern of tonic activity when the cat's view of the target was occluded (Fig. 2*C* and *D*). This result therefore shows that visual feedback is not necessary to maintain the pattern of discharge. Instead, the finding is consistent with the hypothesis that a forward model of target movement has been constructed which predicts the target's velocity and position and thereby maintains neural activity in the absence of sensory information. Such a mechanism is likely to be important for movement planning and control for the interception of a moving object – just the sort of skilled movement that is severely affected when the cerebellum is damaged. Further experiments are required to address the learning process involved in acquiring such models.

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Prometheus' giblets

Chalones were at one time hypothetical factors that once secreted, controlled tissue regeneration and defined its ultimate size. Myostatin is just such a factor and although its ability to attenuate the growth of skeletal muscle is well known, recent studies suggest that it not only regulates cardiac muscle growth, but function as well

Chained to a rock and forced to endure the eternal agony of having his liver ripped from his abdomen and devoured by a winged leviathan, Prometheus may have regretted mankind's gift of fire against Zeus' wishes. Being immortal, he endured this torture daily, for, as we all know, the liver regenerates. Ancient Greeks, by contrast, may not have known of chalones (pronounced 'kay lones', Greek for 'to slacken'), secreted factors that inhibit tissue growth and control the regenerative process, in this case the liver's, but they clearly understood that even titans have bad days.

The chalone–Prometheus association is discussed almost as often as the term chalone itself as both are commonly used to introduce the topic of liver regeneration. This process, however, isn't limited to the liver *per se* as other tissues, skeletal muscle for example, also secrete factors that ultimately limit their growth. Indeed, myostatin is an extremely potent negative regulator of different growth processes that contribute to the size and functionality of skeletal muscle (Rodgers & Garikipati, 2008). The hypermuscularity of the myostatin null phenotype (Fig. 1) has been described in a variety of mammals, including humans, and is responsible for the 'double muscling' that occurs in some domestic breeds. The extreme nature of this phenotype, however, may have overshadowed

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other aspects of myostatin biology that until recently were overlooked.

Several lines of evidence suggest that myostatin may also regulate cardiac muscle (Rodgers & Garikipati, 2008). Its expression was identified in hearts of different mammalian, avian and fish species and it increases progressively as chick hearts develop. It also increases in some models of pathological cardiac hypertrophy. Myostatin inhibits proliferation and protein synthesis in a variety of cardiomyoblast cell culture models and reduces cardiac muscle mass when overexpressed in hearts of transgenic mice (Reisz-Porszasz *et al.* 2003). However, preliminary studies reported conflicting results on differences in heart size between wild-type and myostatin null mice (Rodgers & Garikipati, 2008), suggesting that null hearts could be larger or smaller, depending on sex or age, than wild-type hearts. A more thorough assessment of myostatin's ability to regulate cardiac muscle growth and function was therefore needed.

We recently reported the most comprehensive analysis of myostatin null hearts to date the gestalt of which clearly indicates that myostatin is a negative regulator of physiological cardiac hypertrophy and, for the first time, excitation–contraction coupling (Rodgers *et al.* 2009). Myostatin inhibited basal and insulin-like growth factor (IGF)-stimulated cardiomyoblast proliferation in a dose-dependent manner. It also attenuated retinoic acid-stimulated differentiation while our cell culture system was found to express a full complement of myostatin receptors and binding proteins that matched mature cardiac muscle. Myostatin null hearts, normalized to tail length, were heavier than wild-type hearts at all ages and in both sexes (Fig. 2*A*). These results were confirmed by echocardiography, which also indicated that the larger heart mass was due to eccentric rather than concentric hypertrophy as the internal diameters and volumes were larger in myostatin null hearts despite similar wall thickness measurements (Fig. 2*B*). This is an important distinction as the compensatory response to large increases in skeletal muscle mass, which occurs in myostatin null mice, normally produces concentric hypertrophy. All of these results together indicate that myostatin directly and negatively regulates cardiac muscle growth. They also confirm previous studies with similar conclusions (Rodgers & Garikipati, 2008).

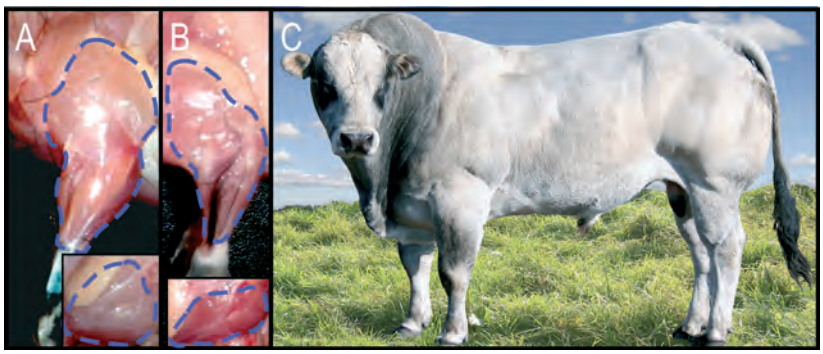

Figure 1. 'Double muscled' phenotype of myostatin null animals. Forelimb musculature of 5-month-old myostatin null (*A*) and wild-type (*B*) mice. Inset are jaw masseter muscles. *C*, Piedmontese bull, the first breed to include a null-genotype (full or partial for *mstn*) as a 'mandatory registry requirement'. Picture reproduced with permission from the North American Piedmontese Cattle Association (NAPA, www.piedmontese.org).

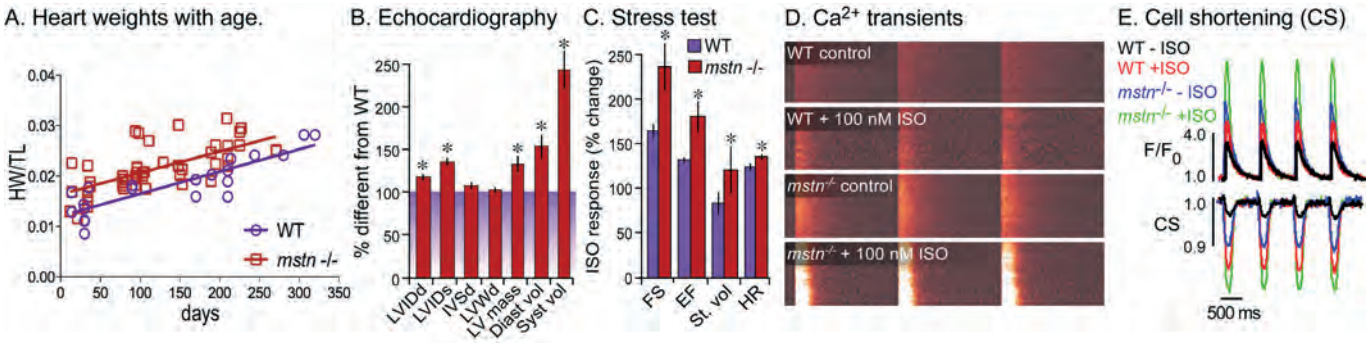

Figure 2. Physiological cardiac hypertrophy and enhanced excitation–contraction coupling in myostatin null hearts (Rodgers *et al*. 2009). *A*, heart weight/tail length (HW/TL) ratios in wild-type (WT) and myostatin null (*mstn*$^{-/-}$) mice of different ages. Female mice are shown, although *mstn*$^{-/-}$ hearts were also larger in male mice. Echocardiography was used to assess cardiac performance and mass in anaesthetized mice before (*B*) and after (*C*) administering 10 mg kg^{-1} isoproterenol (ISO). Data in *C* are represented as % change from before ISO treatment and asterisks denote significant differences in *B* and *C* ($P \leq 0.05$). LVIDd/s, left ventricle internal diameters at diastole and systole; IVSd, intraventricular septum; LVWd, LV wall dimension; Diast and Syst vol, LV end diastolic or systolic volume; FS, fractional shortening; EF, ejection fraction, St. vol, stroke volume; HR, heart rate). *D*, confocal line scan images of evoked $[Ca^{2+}]_i$ transients (1 Hz) in WT and *mstn*$^{-/-}$ ventricular myocytes before and after (–/+) 100 nM ISO. *E*, time course of $[Ca^{2+}]_i$ (top) and cell shortening (CS) in representative WT and *mstn*$^{-/-}$ ventricular myocytes before and after ISO. Transients were evoked with field stimulation (1 Hz).

Most notably, we also discovered that myostatin null cardiac muscle was functionally superior to that of wild-type mice during an isoproterenol (ISO) stress test. In fact, changes in ISO-stimulated cardiac output, as indicated by several parameters (Fig. 2*C*), were significantly greater in myostatin null mice. This included heart rate and suggested that excitation–contraction coupling may also be enhanced. We confirmed this hypothesis *in vitro* using several biophysical assays and ultimately determined that $[Ca^{2+}]_i$ transients (movements between intracellular stores) and total cellular loads were greater in primary ventricular myocytes from myostatin null hearts. Furthermore, these differences were associated with enhanced contractility in isolated cells (Fig. 2*D* and *E*). The superior β-adrenergic responsiveness and cardiac output in myostatin null hearts was therefore due in part to differences in Ca^{2+} handling and excitation–contraction coupling.

Normalized tension, ATPase activity and the tension–cost relationship of skinned fibres from wild-type and null hearts were identical and previous studies determined that the latter were histologically normal. We additionally determined that myostatin null hearts do not possess the fetal gene expression profile that occurs when hearts hypertrophy from pathological conditions, as with chronic hypertension or following myocardial infarction. Cardiac hypertrophy itself is not inherently bad as it is also an adaptive response to exercise. Myostatin null mice, therefore, possess physiological, not pathological, cardiac hypertrophy.

Myostatin-blocking technologies (e.g. immunoneutralization, soluble receptors, etc.) are currently being developed in both academic and industrial labs and all have produced very promising results (Rodgers & Garikipati, 2008). None, however, has thoroughly explored their potential in treating cardiac pathologies, and have focused primarily on muscular dystrophies and sarcopenia. Recent studies also suggest that attenuating myostatin action could potentially improve insulin sensitivity and reduce fat mass in obese subjects, most probably by increasing muscle mass and as a consequence, the resting energy expenditure (Guo *et al.* 2009). It is not unreasonable, therefore, to presume that such myostatin-blocking technologies may also help treat a variety of cardiac pathologies as well as two exacerbating conditions – obesity and type 2 diabetes.

The liver may be the most fabled regenerative organ. However, it is not alone as most organs possess at least a limited capacity to regenerate some or all of their tissues. This includes another giblet, the heart, whose growth is regulated by the chalone myostatin. One has to imagine, therefore, whether Prometheus would have suffered less had he lacked myostatin. He would have at least been in better shape to fight off that wretched bird.

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Bloodless revolution

Subtle paracrine interactions between minor depots and contiguous tissues are restoring the reputation of adipose tissue, best known for its bulk and disease-causing properties. Micromanagement of fatty acids supports fast, efficient immune responses that avoid competition with other lipid-utilizing tissues. Such roles explain aspects of the gross anatomy of mammalian adipose tissue, long thought to be inexplicable

Aversion to adipose anatomy

Adipose tissue's 'image' has had a more thorough 'makeover' during the past 15 years than that of any other organ or tissue. For physiologists, proteomics and the enthusiasm of the pharmaceutical industry have made secreted peptides, leptin, visfatin, resistin, adiponectin and many more, the best-known aspect of this revolution. But at last, anatomists are trying to explain the tissue's organisation and anatomical relations, topics that concern surgeons, beauticians and ordinary people dissatisfied with their figures but not with their body mass.

One of the major triumphs of biology between the late eighteenth century and mid-twentieth century was showing that the arrangement of major organs in each group of animals follows a consistent body plan. In cases such as snakes and whales, where one or both pairs of limbs are absent, remnants are detectable during development and sometimes throughout life as vestigial structures. Many of the *hox* genes controlling these major anatomical changes have been identified. But many adipose depots seem to appear and disappear without such formalities, capricious variation that demoralised comparative anatomists: the topic is not addressed in Edwin Goodrich's 1930 treatise, *Studies on the Structure and Development of Vertebrates*. This omission led to the notion that its distribution and anatomical relations are without functional or phylogenetic significance. Goodrich's distaste for anatomically unruly tissues, plus the widening gap between comparative and functional anatomy and rising concern about obesity, focussed attention on just one or two large, readily accessible adipose depots. Except for a few

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obvious deviants like metabolically inert, structural depots, all adipose tissue was presumed to respond similarly to blood-borne and neural signals.

Lymphoid structures of all endothermic vertebrates are closely associated with adipose tissue (Pond, 2003). In mammals, the lymph ducts run through the adipose tissue and divide into numerous fine branches near the nodes, thereby coming into contact with many of the surrounding adipocytes. The omentum, a uniquely mammalian structure, is a patchwork of adipose and immune cells. Under the insidious influence of adipose-aversed anatomists (Fig. 1), most textbooks of immunology described these facts very briefly, if at all (Harvey, 2008).

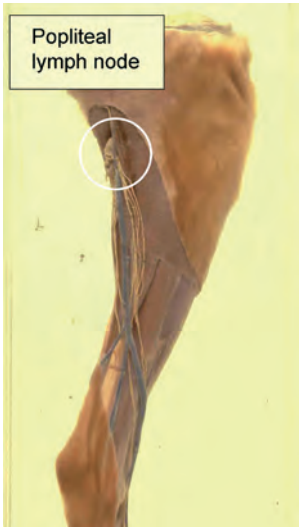

Figure 1. The source of the problem. 19th century prosection made for The Royal College of Surgeons' Hunterian Museum of the popliteal 'space' in the right hind leg of a dog, showing the 'important' components of the lymph and blood systems. Blood vessels and lymph nodes shorn of their adipose tissue still feature in modern textbooks, perpetuating the misleading notion that perivascular and perinodal adipose tissue are irrelevant or abnormal.

In the early 1990s, the study of neurohumoral activity of perivascular adipose tissue around rat aorta was prompted by the observation that 'virtually every blood vessel in the body is surrounded to some degree by adipose tissue' (Soltis & Cassis, 1991). At about the same time, we began to investigate experimentally why epicardial and pericardial adipocytes (Marchington *et al*. 1989; Marchington & Pond, 1990) develop early in life and are not depleted in naturally lean wild animals. We were stumped by the most basic problem: laboratory rodents have variable, often negligible, quantities of cardiac adipose tissue. Advances in MRI and other scanning systems at the new millennium enabled the site-specific properties of these minor adipose depots to take centre stage in clinical and basic cardiovascular physiology (Iacobellis *et al*. 2008). Although long regarded as pathological, the cardiac depots are at last achieving respectability as integral, natural components of the heart (Fox *et al*. 2009); perinodal adipose tissue deserves similar status.

Minor depots, major players: lipids for lymph nodes

Many, possibly most, of the fatty acids incorporated into lipids in lymph node lymphoid cells that are newly formed in response to immune stimulation are derived from triacylglycerols in perinodal adipocytes (Pond, 2007, 2009). Site-specific properties of perinodal adipocytes equip them to supply

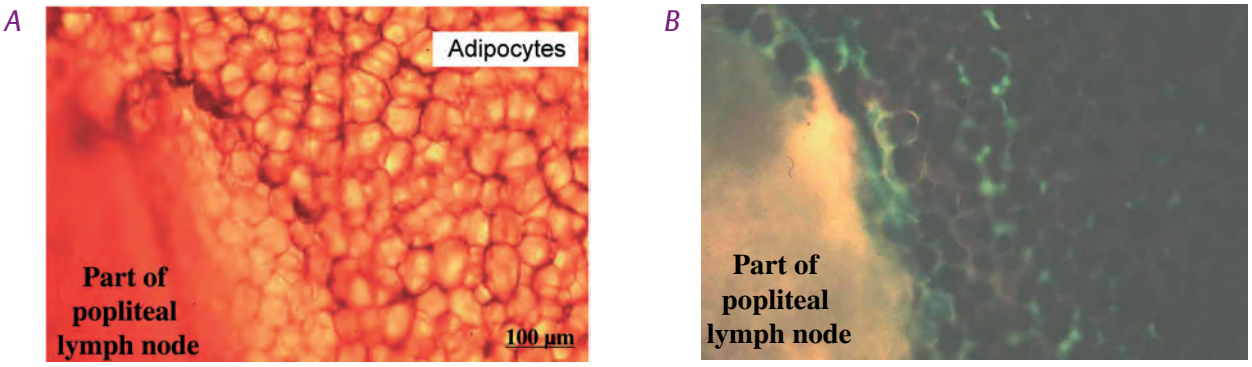

Figure 2. Perinodal adipose tissue functions as part of the lymph node. Thick section of part of a rat popliteal lymph node and its perinodal adipose tissue 1 h after subcutaneous injection of 2 mg lipopolysaccharide and staining with immunofluorescent antibody to type 1 receptors to tumour necrosis factor-α seen under (*A*) bright field (*B*) UV light. Perinodal adipocytes are indistinguishable from others until cytokine receptors appear on the surface, some within minutes of activation of the enclosed lymph node (MacQueen & Pond, 1998).

lymphoid cells. Spontaneous lipolysis in adipocytes within 2 mm of lymph node(s) draining the site of the immune stimulus increases within an hour of an experimentally elicited immune response, reaches a maximum after about 6 h and then wanes, disappearing totally after about 24 h. But the effect can be prolonged, possibly indefinitely, and elicited in adipocytes situated further from the lymph node, by repeated immune stimulation. The appearance of more receptors for tumour necrosis factor-α on perinodal adipocytes follows a similar time course (Fig. 2). Perinodal adipocytes respond much more strongly than those not anatomically contiguous to lymphoid structures to tumour necrosis factor-α, interleukin-4 and interleukin-6 and probably other cytokines. These signal molecules may mediate the paracrine interactions between adipocytes and the lymphoid cells that they supply.

Lymph node-derived dendritic cells suppress lipolysis in perinodal adipocytes but those that permeate the adipose tissue stimulate lipolysis, especially after minor, local immune stimulation enabling lymph node lymphocytes and tissue dendritic cells to acquire fatty acids from the contiguous adipocytes. Their triacylglycerols contain more long-chain polyunsaturated fatty acids, precursors for eicosanoids and docosanoids. Chronic inflammation alters their composition, and hence that of the lymphoid cells they supply, counteracting adverse effects of dietary lipids.

The involvement of perinodal adipocytes in immune responses not only begins within minutes but can persist for months. In a rat experiment to explore recovery from simulated low-level chronic inflammation, the numbers of dendritic cells recovered from the locally stimulating lymph node and its perinodal adipose tissue rose at least tenfold within 4 weeks and remained higher long after this regime was applied (Fig. 3). Perhaps surprisingly, perinodal adipose tissue around remote lymph nodes, especially those in the abdomen, responded similarly (Fig. 4).

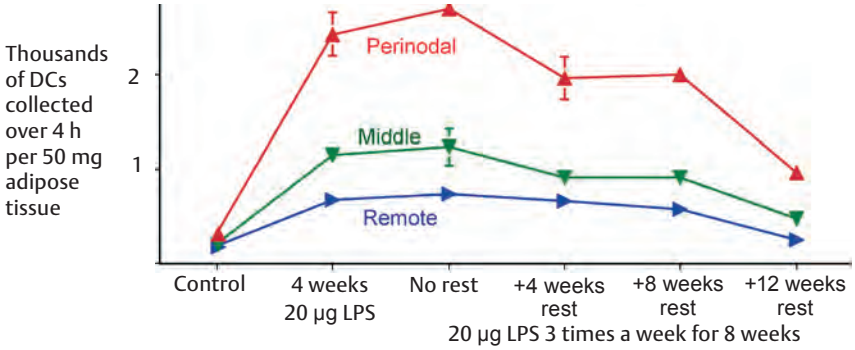

Figure 3. Perinodal adipose tissue stays alert. Mild chronic immune stimulation (local subcutaneous injection of 20 mg lipopolysaccharide (LPS) 3 times a week) increases interchelated dendritic cells (DCs) throughout the popliteal adipose depot, most in the perinodal, within 2 mm of the large popliteal lymph node, but significant in the 'middle' sample, about 5 mm from the node, and the 'remote' sample more than 10 mm away. Recovery is surprisingly slow: numbers of CCL21 (C6kine)-activated dendritic cells migrating from tissue samples are still higher more than 8 weeks after experimental inflammation ended. (Data from Sadler *et al*. 2005.)

Prolonged, low-level immune stimulation induces the local formation of more adipocytes, especially adjacent to the inflamed lymph node. This mechanism may contribute to hypertrophy of the mesentery and omentum in chronic inflammatory diseases such as HIV infection, and in smokers. The site-specific differences in fatty acid composition of lipids in the mesenteric adipose tissue expected from animal studies are absent from Crohn's disease patients, though they were found in similar samples from the controls (Westcott *et al*. 2005). The composition of lymphoid cells in mesenteric lymph nodes resembles that of the adjacent perinodal adipose tissue in the controls, but not in the diseased patients, which suggests that their adipocytes are not supplying fatty acids to cells in the adjacent lymph nodes. Lipids from the lymph node lymphoid cells from Crohn's disease patients contain much less of the eicosanoid precursor arachidonic acid (C20:4*n*-6) than the controls.

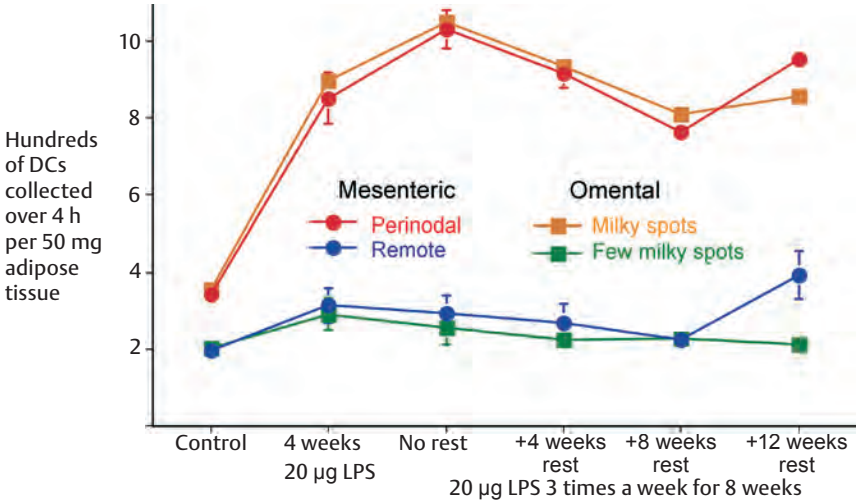

Figure 4. Even remote, mild inflammation gradually gets to the guts. Mild chronic immune stimulation of the skin over the hind leg increases interchelated dendritic cells in the adipose tissue around remote as well as local lymph nodes. This effect is substantial in the mesentery and milky spot-rich areas of the omentum, where it persists for at least 3 months after experimental inflammation ends, but is almost undetectable in the more frequently sampled mesenteric adipose tissue located more than 10 mm from a lymph node. It may be among the ways that chronic or repeated inflammation slowly induces hypertrophy of intra-abdominal adipose tissue. (Data from Sadler *et al*. 2005.)

The discrepancy between the composition of perinodal adipocytes and that of adjacent lymphoid cells contrasts with the concept of paracrine nutrition of lymphoid cells, but is consistent with reports that blood-borne mononuclear cells from Crohn's disease patients contain more, not less, n-3 polyunsaturated fatty acids. General defects in perinodal adipose tissue leading to impaired immune function could explain the association between the bowel disorders and other chronic diseases such as arthritis, eczema and rhinitis (Book *et al*. 2003). Could 'fat wrapping', the distinctive but as yet unexplained feature of Crohn's disease, be adipose tissue's long-term response to persistent signals from its client immune cells for important fatty acids that it is unable to supply?

Paracrine provision: private, personalised, potent

By ensuring that specific, possibly scarce, fatty acids reach the cells that really need them when and where required, perinodal adipocytes may be compared to tRNA that marshals amino acids into position or chaperonins that help proteins fold correctly. Local provisioning of lymphoid tissues partially emancipates immune function from fluctuations in food quantity and composition. Energy-consuming systemic responses to immune challenges, such as fever, avoid competition for essential lipids with proliferating lymphoid cells; anorexia may help to 'put adipose tissue in charge' of lipid management during the crisis. Supplying fatty acids of slightly different composition also provides local sources of structural, and perhaps also functional, diversity of lymphoid cells that hitherto have been classified by genes and proteins (Gehring *et al*. 2008). Paracrine interactions, especially those involving only a small fraction of the total adipose tissue, cannot easily be detected as changes in blood composition. But blood supply to perinodal adipose tissue increases during inflammation so they could probably be manipulated by blood-borne drugs.

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Acknowledgements

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Exercise-induced lipid mobilization in humans: the role of catecholamines revisited

Bidirectional communication exists between the central nervous system and white adipose tissue. Here we discuss the relative contribution of the various factors involved in exercise-induced lipid mobilization in humans, reassessing the role of catecholamines

A number of questions concerning the regulation of lipid mobilization (i.e. hydrolysis/lipolysis of triglycerides stored in the adipocytes) have been mostly investigated in rodents, the adipose tissue of which clearly differs from that of humans. Lipolysis is such an important metabolic event that a number of redundant factors and pathways contribute to its physiological regulation (Lafontan & Langin, 2009) (Fig. 1). The debated questions concerning the role of the sympathetic nervous system in the control of white adipose tissue lipolysis have recently been reviewed by Bartness *et al.* (2009). White adipose tissue is innervated by the sympathetic nervous system but at very low levels of innervation of adipocytes. Moreover, the sympathetic nervous system drive to the various body fat deposits is not homogenous. In humans, up until recently, the major regulators of lipid mobilization (i.e. hydrolysis of triglycerides stored in the adipocytes) were considered to be the catecholamines (adrenaline (ephinephrine) and noradrenaline (norepinephrine)) as the stimulators of lipolysis and insulin for its inhibition.

In humans, the unquestionable impact of both catecholamines on lipid mobilization is observed when they are infused intravenously. However, the relative contribution of both amines in the physiological

Vladimir Stich (left) and Max Lafontan

control of lipid mobilization during physical exercise has been less convincingly established. Exercise is an excellent physiological challenge to promote sympathetic nervous system activation; there is no doubt that it contributes to the control of lipid mobilization, since plasma levels of adrenaline and noradrenaline are increased during exercise. They stimulate both fat cell $\beta_{1\text{-}2}$- and α_{2A}-adrenergic receptors, which enhance and inhibit lipolysis, respectively. In fact, the simultaneous activation of both receptors modulates the intracellular cAMP concentration, which activates cAMP-dependent protein kinase, leading to the phosphorylation and activation of the hormone-sensitive lipase (Lafontan & Langin, 2009). Growth hormone (GH) and other putative lipolytic candidates (i.e. natriuretic peptides or IL-6) have also been suspected to contribute (Fig. 1). In addition, exercise is also well known to promote inhibition of insulin release that is related to sympathetic nervous system-mediated inhibition of insulin release at the level of the pancreatic β-cells. Suppression of the anti-lipolytic effect of insulin is important to enhance the lipolytic activity of the fat cells. Nevertheless, contrary to former beliefs, studies have questioned the importance of the contribution of catecholamines. It has been shown, at low and moderate intensities of exercise, that under an oral β-adrenergic receptor blockade associated with a local perfusion of propranolol, the exercise-induced increase of

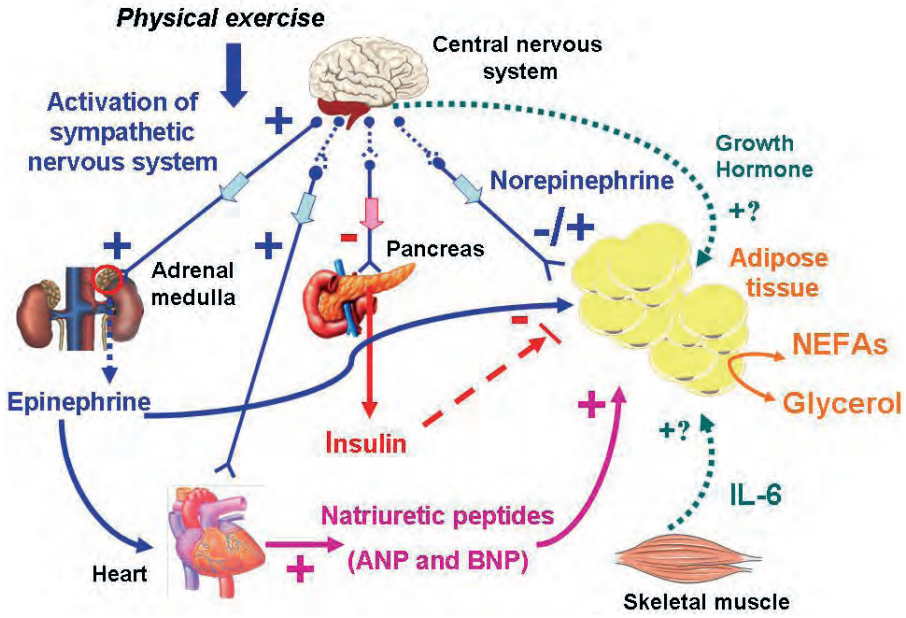

Figure 1. Hormonal factors involved in the control of exercise-induced lipid mobilization in humans. Catecholamines (adrenaline and noradrenaline) can act on fat cell $\beta_{1,2}$- and α_{2A}-adrenergic receptors according to a complex interplay (see Fig. 2) and promote acute stimulation of lipolysis (see discussion). Natriuretic peptides (ANP and BNP) are released by the heart cardiomyocytes during exercise. Their release is increased after the oral administration of a β-adrenergic receptor antagonist given before exercise. The secretion of insulin, the potent anti-lipolytic hormone, is suppressed by noradrenaline released during physical exercise. Growth hormone (GH) is also released by exercise but its effect on lipid mobilization is not acute. Increased circulating interleukin-6 (IL-6) levels observed during exercise originate from skeletal muscle; the lipolytic effect of IL-6 is weak and not acute. Neither agent (GH and IL-6) can be considered to contribute to the regulation of lipid mobilization under the experimental conditions used by de Glisezinski *et al.* (2009).

lipolysis was diminished but not completely inhibited (Moro *et al.* 2004). Based on previous studies demonstrating the lipolytic role of natriuretic peptides (Sengenes *et al.* 2000) (Fig. 2), the residual lipolysis remaining under full β-adrenergic receptor blockade was attributed to these peptides. In fact, plasma levels of natriuretic peptides increase during an acute bout of physical exercise, and an enhanced release of these peptides occurs when exercise is performed under oral β-adrenergic receptor blockade (Moro *et al.* 2004). Further studies have shown that natriuretic peptides are physiological contributors of exercise-induced lipid mobilization in various situations in humans, though this system is not operative in rodents and dogs (Lafontan *et al.* 2008).

The relative contribution of the various factors involved in the control of exercise-induced lipid mobilization still remains an open and intricate challenge. A recent study investigating this complex question has allowed the delineation of the relative contribution of adrenaline and noradrenaline in the control of exercise-induced lipid mobilization in man to be elucidated (de Glisezinski *et al.* 2009), and revealed the importance of adrenaline instead of noradrenaline.

A pharmacological strategy was used to support this physiological approach and eliminate the intervention of some factors. Firstly, the catecholaminergic responsiveness was studied when insulin and GH secretions were suppressed. An intravenous infusion of the somatostatin analogue, octreotide, was given before, during and after exercise; it potently inhibited insulin and GH secretion during exercise. In addition, the noticeable point was that adrenaline secretion was also blocked by octreotide treatment while the exercise-induced increase in noradrenaline release was not modified (Fig. 3c). Thus, octreotide administration provides a unique condition whereby the impact of adrenaline and noradrenaline on lipolysis could be dissociated. Experiments were performed on healthy lean young men, fasted overnight and performing exercise bouts over 60 min at 50% of their peak oxygen uptake during placebo or octreotide administration.

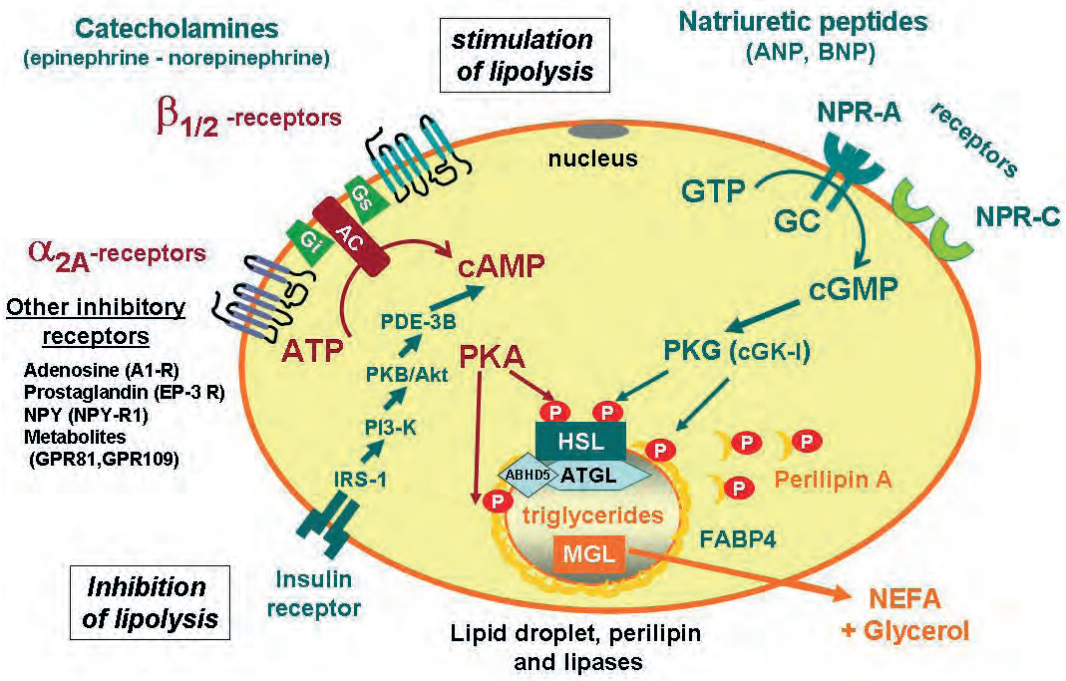

Figure 2. Major pathways involved in the stimulation of human fat cell lipolysis. Signal transduction pathways for catecholamines via $\beta_{1\text{-}2}$- and α_{2A}-adrenergic receptors, autacoids- and metabolite-driven inhibitory receptors and atrial natriuretic peptides (ANP and BNP) via type A receptor (NPR-A). Protein kinases (PKA and PKG (cGK-I)) are involved in target proteins phosphorylation (perilipin and HSL). ATGL possesses an exclusive triglyceride lipase activity; it is activated by ABHD5. Perilipin phosphorylation induces an important physical alteration of the lipid droplet surface that facilitates the action of ATGL and HSL on triglycerides and the initiation of lipolysis. Perilipin phosphorylation also releases ABHD5, the activator of ATGL. HSL phosphorylation promotes its translocation from the cytosol to the surface of the lipid droplet. MGL hydrolyses monoacylglycerols. Docking of adipocyte lipid binding protein (FABP4) to HSL favours the outflow from the cell of NEFAs released by the hydrolysis of triglycerides. Glycerol outflow is facilitated by aquaporin-7 present in the adipocyte. Insulin, via stimulation of fat cell insulin receptors and phosphodiesterase-3B (PDE-3B) activation, promotes cAMP degradation and anti-lipolytic effects. It is not active on cGMP-dependent pathways (not shown in the diagram). ABHD5, αβ-hydrolase domain-containing protein; ANP, atrial natriuretic peptide; ATGL, adipose triglyceride lipase; BNP, B type natriuretic peptide; FABP4, adipocyte fatty acid binding protein 4; GC, guanylyl cyclase; Gi, inhibitory GTP-binding protein; Gs, stimulatory GTP-binding protein; HSL, hormone-sensitive lipase; MGL, monoacylglycerol lipase; NEFA, non-esterified fatty acid; NPR-A, type A natriuretic peptide receptor; NPR-C, type C natriuretic peptide receptor.

Microdialysis was used to monitor local lipid mobilization (i.e. glycerol release) in subcutaneous adipose tissue during the exercise. It is a well-recognized method for mechanistic explorations of adipose tissue responsiveness *in vivo*.

Local blockade of fat cell β- and α_{2A}-adrenergic receptors was carried out *in situ* by direct perfusion of the β- (i.e. propranolol) and α_{2A}- (i.e. phentolamine) antagonists through the microdialysis probes to investigate the part played by catecholamines during exercise. The physiological stimulation of adipocyte α_2-adrenergic receptors during exercise-induced sympathetic nervous system activation contributes to the blunted lipolysis. Phentolamine suppresses the blunting effect of α_{2A}-adrenergic receptor stimulation. The blockade of α_{2A}-adrenergic receptors removes the lipolysis-inhibiting part of the catecholamine action during exercise (Stich *et al.* 2000). If, in addition to that, when the local β-adrenergic receptor blockade was performed, the exercise-induced lipolysis was reduced in control (Fig. 3a) but not in the octreotide condition (Fig. 3c). This suggests that the β-adrenergic stimulation of lipolysis during exercise is mediated by adrenaline but not noradrenaline. In fact, both plasma levels of adrenaline and noradrenaline 'normally' increase when physical exercise is performed in control conditions. Under octreotide infusion the exercise-induced increase of plasma adrenaline is completely blocked while noradrenaline increment persists (Fig. 3c).

Based on these results and on some previous studies (Stallknecht *et al.* 2001), it is suggested that it is plasma adrenaline rather than noradrenaline which is the main adrenergic factor involved in exercise-induced lipolysis, at least in human subcutaneous adipose tissue. It must be remembered that adrenaline is known to possess the highest affinity, when compared with noradrenaline, for β_2- and α_{2A}-adrenergic receptors, the major adrenergic receptors of the human adipocytes (Lafontan & Berlan, 1982). In addition, the persistence of lipid mobilization after the full blockade of fat cell adrenergic receptors suggests

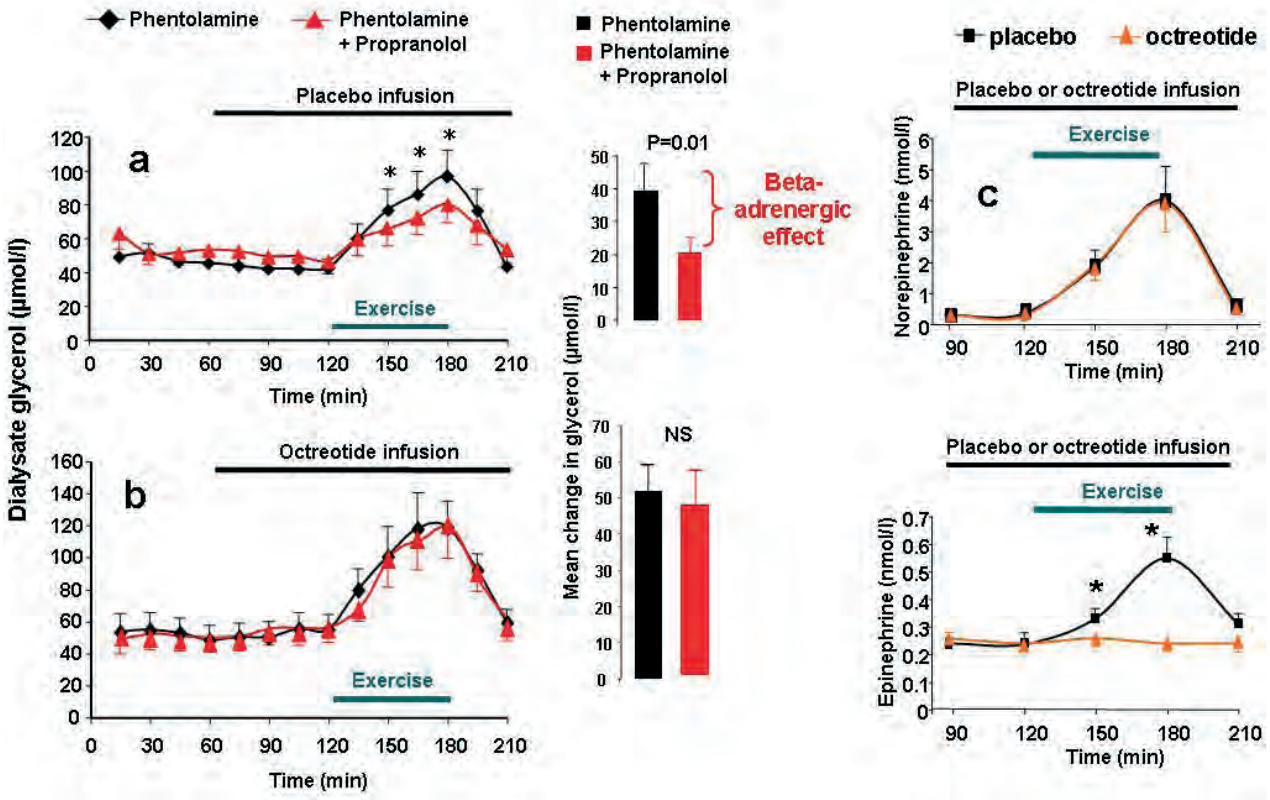

Figure 3. Impact of physical exercise (60 min at 50% of peak oxygen uptake) on lipid mobilization in placebo or octreotide-treated lean human subjects. Dialysate glycerol concentration from subcutaneous adipose tissue measured at rest, during exercise and the recovery period under intravenous infusion of placebo (a) or octreotide administration (30 ng^{-1} min^{-1} kg^{-1}) (b) in lean subjects. One probe was perfused with Ringer solution plus phentolamine (100 μmol l^{-1}) and the second one with Ringer solution plus phentolamine (100 μmol l^{-1}) plus propranolol (100 μmol l^{-1}). Data are expressed as mean ± S.E.M. $^*P < 0.05$, significant when compared to values obtained in the probe with phentolamine plus propranolol and the probe with phentolamine alone. c, plasma noradrenaline and adrenaline (norepinephrine and epinephrine) concentrations at rest, during exercise and the recovery period under intravenous infusion of placebo or octreotide (30 ng min^{-1} kg^{-1}) in lean subjects. Data are expressed as mean ± S.E.M. $^*P < 0.05$, significant when compared to values obtained with octreotide infusion. Octreotide treatment suppresses exercise-induced adrenaline release while having no impact on noradrenaline release (c). When adrenaline is not released, the β-adrenergic component of the lipid mobilizing response disappears completely although plasma noradrenaline levels are elevated.

that, as previously mentioned, it is the natriuretic peptides which constitute the lipid-mobilizing factor responsible for the exercise-induced lipid mobilization in subcutaneous adipose tissue (Lafontan *et al.* 2008). This study is focused on the importance of circulating factors (i.e. adrenaline, insulin and natriuretic peptides) in the control of exercise-induced lipid mobilization in human subcutaneous adipose tissue. The sympathetic drive to white adipose tissue differs according to fat deposits and so the importance of innervation-mediated effects *versus* adrenaline effects could produce some variability. Nevertheless, coming before the hormonal hypothesis, both the denervation approaches and direct sympathetic nerve stimulation support a role for sympathetic innervation in the initiation of lipolysis in rodents and humans. We must keep in mind that these procedures have a tendency to affect both sympathetic nerve fibres but also sensory fibres present in the nerves that could interfere in the control of energy stores (Bartness *et al.* 2009).

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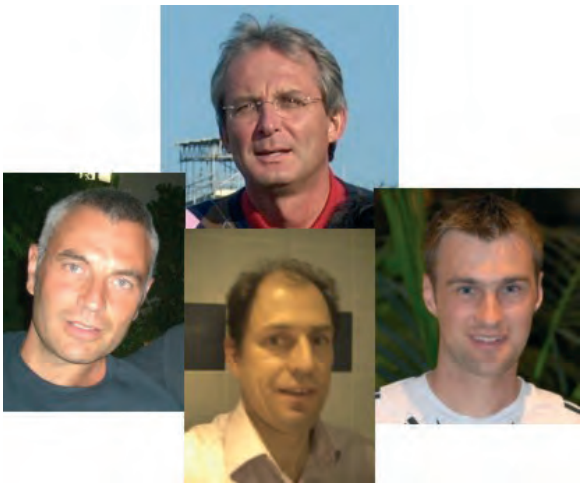
Work against gravity: in search of the molecular switch for mechano-regulated muscle plasticity

Prolonged reductions in weight-bearing muscle activity during bedrest or spaceflight cause dramatic loss in strength due to wasting of postural muscle. Astonishingly little is known concerning the mechano-sensory pathways which underpin this response. Our recent work addresses the process of mechano-transduction by using somatic transgenesis and altered loading to modify the putative mechanoreceptor

Work-related stimuli are critical for maintenance of muscle function (Loughna & Goldspink 1990). This physiological control is apparent in the dramatic loss of force and metabolic capacity associated with reductions in muscle loading during real or simulated microgravity, and the reversal of these deteriorations with subsequent resumption of load-bearing muscle activity. These responses highlight the instrumental role of mechanical factors in the conditioning of muscle structure and function. In contrast to the accepted clinical importance of this mechano-dependent muscle plasticity and identified mechano-sensible signalling factors (Nader & Esser, 2001) there is a distinct lack of understanding of the signalling mechanisms *in vivo*.

Focal complexes of proteins have been proposed to convert the mechanical factors of contraction into biochemical signalling inside muscle fibres (Fig. 1; Lange 2005; Durieux *et al*. 2009). This idea is based on the association of focal adhesions with specific signalling molecules in cultured muscle cells (Shyy & Chien, 1997) and the architectural coupling of sarcolemma sites of fibre adhesion (costameres) with sarcomere shortening during muscle contraction (Pardo *et al*. 1983). The functional involvement of costameres in mechano-transduction and phenotypic control of fully differentiated striated muscle is largely unexplored. This may be because integrin receptors which form the adhesive core of costameres are devoid of enzymatic activity. Indirect observations suggest that mechano-transduction is initiated by strain-induced conformational changes in integrins (Katsumi *et al*. 2005) and the subsequent coupling to intracellular signalling (reviewed by Durieux *et al*. 2009). The kinase enzymes involved in this response have, until lately, not been characterized.

Our recent investigation addressed this topic by focusing on the role of the integrin-associated phosphotransfer enzyme focal adhesion kinase (FAK; Durieux *et*



Team members from the University of Berne, University of Pavia and Manchester Metropolitan University who contributed to the characterisation of contractile consequences of FAK overexpression. From left to right, Giuseppe D'Antona, Roberto Bottinelli (top), Martin Flück (bottom) and Stephan Klossner.

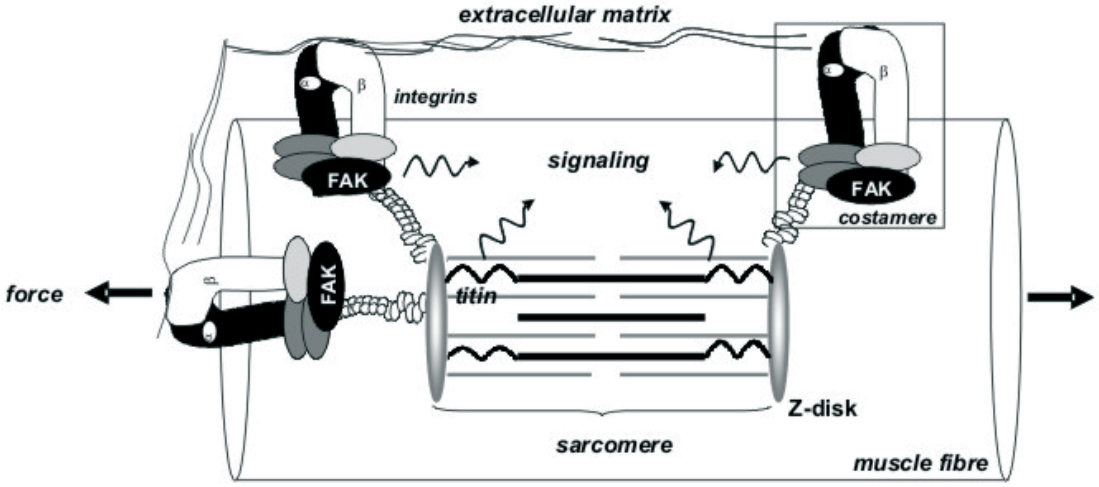


Figure 1. Model outlining the role of costameres in the physical coupling of sarcomere shortening with the sarcolemma and the conversion of contractile forces into biochemical signalling (wavy arrow). For completeness, signalling initiated within the mechano-sensory kinase domain of titin is also indicated.

al. 2009). In cultured cells, FAK is involved in mechano-chemical coupling between mechanical stimulation of integrins and intracellular signal transduction. Phosphorylation of FAK at tyrosine residue 397 (Y397) is considered to reflect activation of FAK and downstream signal transduction (Shyy & Chien, 1997). The role of this signalling molecule in mechano-transduction in intact tissue had so far not been investigated owing to the lethal consequences of FAK inactivation via the germline. Our study addressed this question using somatic technology which allowed overexpression of FAK in fully developed anti-gravitational muscle. The loading state of the muscle was physiologically modulated in a ground-based model of microgravity (hindlimb suspension) and muscle loading (tenotomy; Fig. 2). The monitoring of transcriptional, myocellular and contractile consequences pointed out myofibre transformation with the overexpression of full-length FAK in soleus muscles towards a slow-oxidative phenotype. Competition experiments with the combined overexpression of a FAK inhibitor (FRNK) demonstrated the specificity of FAK-regulated transcript expression. Probing with a native, rather than a constitutively active, FAK protein exposed the post-translational activation of FAK by phosphorylation at tyrosine Y397 as a molecular switch of mechano-regulated muscle plasticity (Durieux *et al*. 2009).

Our findings compare well with recent findings on the down-regulation of the activation status of FAK during muscle disuse atrophy in humans (de Boer *et al*. 2007) and FAK-mediated activation of the S6Kinase-dependent pathway (Klossner, 2009). These observations indicate that costamere-mediated mechano-transduction is involved in the anabolic control of muscle mass. It remains to be determined to what degree this mechanism is selective for activation of muscle protein synthesis or whether it controls protein turnover in general. This possibility was suggested by the mechano-modulated control of expression of the gene ontologies for protein degradation by FAK (Durieux *et al*. 2009).

The outlined experimental approach (see Fig. 2) provides an important step forward towards the investigation of signal integration in a fully developed tissue. The success of the experiments relied on the exceptional capacity of muscle for uptake of naked DNA upon electropulsing, and the monitoring of downstream consequences of overexpression with a combination of classical and modern technologies. We reason that this set-up may be of generic interest to muscle research as it offers a ready, low-cost alternative to labour-intensive and expensive transgenic approaches via the germline. The electro-assisted muscle transfection technique also has the benefit of reducing biological noise by allowing the inclusion of intra-animal, i.e. contralateral, controls in paired muscle groups. This advantage was shown in somatic knock-in experiments exposing the hitherto unknown consequences of mechano-regulated extracellular matrix protein expression in muscle repair (Flück *et al*. 2008). The transfection tool therefore fills a gap for the researcher wishing to explore mechanistic relationships with a tight budget or timeline,or in animal species which do not lend themselves to efficient transgenic modification with germline technology.

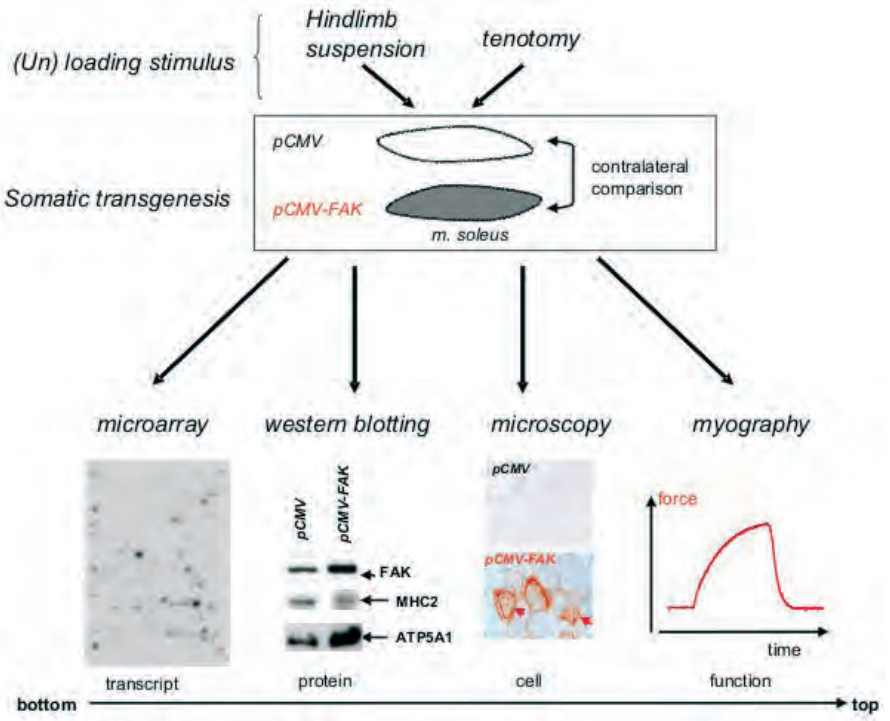


Figure 2. Scheme illustrating the integrative bottom-up approach to investigate the role of FAK in mechano-dependent muscle regulation. The techniques employed are given in italics and selected results are included. Central to this approach was the comparison between contralateral soleus muscle pairs of rats being transfected with empty plasmid (pCMV) or plasmid for full-length focal adhesion kinase (pCMV-FAK). MHC2, combined fast myosin heavy chains; ATP5A1, subunit of complex five of the respiratory chain. The interested reader is referred to the original article in *The Journal of Physiology* (Durieux *et al*. 2009).

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Dear Sir

The article by Launikonis *et al*. (*Physiology News* **77**, 20) was interesting. I took skeletal muscle physiology for undergraduate students for the last couple of years which earned me the nickname of 'muscle man', though in reality I have more fat than muscle. During these classes I used to stress that calcium release in the skeletal muscle is voltage induced (VICR) and that in the cardiac muscle is calcium induced (CICR). However, I used to wonder whether calcium would enter the skeletal muscle through the dihydropyridine receptors in the T-tubule. Store-operated calcium entry in skeletal muscle has been previously reported (Grimaldi *et al*. 2001). The discovery of action potential-activated calcium current will probably add to a growing list of calcium entry pathways yet to be discovered in the skeletal muscle. I hope that further research will be done in this area to find the physiological significance of these modes of calcium entry in the skeletal muscle.

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Esoteric activities

Students hesitating about taking a physiology course may be told it is a discipline that can accommodate many talents. Some time ago, during the display of final year (Part II) posters in Cambridge, I asked one of the Natural Scientists what he'd be doing next. He replied that he was going to be a concert pianist. The next I heard of him was as winner of Radio 2's Young Musician of the Year. Another unexpected talent came to light at the funeral of the late David Whitteridge who had held the Chairs of Physiology at Edinburgh and Oxford. The Vicar of St Giles Church in Oxford revealed that he had been an expert on the romantic novels published by Mills & Boon. Apparently these usually formed a large part of the stock on the Book Stall that David so knowledgably manned at the Church Fête. And on Boxing Day 2009 The Society's oldest Member, Andrew Huxley, had a new role as one of the judges at the annual inter-pub Barrel Rolling Race held in Grantchester, outside Cambridge.

Ann Silver

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On reading the amusing article 'Why I hate epigenetics' (*Physiology News* **77**, Winter 2009, p. 43) Denis Noble dreamt that he was the Editor and had received the following letter, which he then translated into English for the benefit of readers of *Physiology News*:

Jardin des Plantes,
Paris, le 21 novembre 2009

Monsieur l'éditeur

I had no idea that my scientific ideas were to become so politically sensitive, though I have been told that the distinguished Edinburgh professor of genetics and developmental biology, Conrad Waddington, was ignored by his fellow American scientists during the McCarthy inquisitions of the mid-20th century because of possible association with something called Communism, largely because he invented the term 'epigenetics' and claimed to have shown that it confirmed my ideas on inheritance. He called those ideas 'lamarckism' and was certainly not the first to do so. That damnable giraffe's neck (!) keeps returning to haunt me, whereas I thought I would be remembered for having introduced a new scientific subject, which I called biology (I was the first to do so), and for demonstrating the transformation of species and, hence, the basic truth of evolution.

I am deeply puzzled by the term 'lamarckism' for another reason also. Your brilliant Honorary Member, Charles Darwin, elected to that position on the foundation of your esteemed Society in 1876, also espoused the idea that acquired characteristics could be inherited [DN: see note 1]. In fact, like all biologists of our time, and even earlier, we absorbed this idea from our predecessors. I am amused that an idea for which I was not the inventor should have become so strongly associated with my name. I may be a 'demented gloating little troll' – in fact, I died so poor that they had to throw my body into a common lime-pit – but I can't quite see why I am associated with the idea any more than Mr Darwin. He never disagreed with me on this issue, since neither of us knew anything about the later discoveries of genetics that seemed to exclude it. He even introduced the idea of gemmules, particles that he imagined to flow through the blood stream to communicate acquired characteristics to the reproductive organs. Incidentally, your modern ideas on micro-chimerism are not so far from his idea of gemmules. It isn't just epigenetics that is resurrecting the idea of the inheritance of acquired characteristics, nor would Mr Darwin be surprised. I have it on good authority that he was uncomfortable with the dogmatism of those who usurped his name by calling themselves neo-darwinists. [DN: see note 2]

No, the main issue on which Mr Darwin and I disagreed was whether there was a direction to evolution, what I called 'le Pouvoir de la Vie'. This was not a mystical concept. In fact, I thought of it as derivable from basic physical principles, and so a perfectly natural phenomenon. Some of your modern ideas on complexity are not far removed from what I was thinking. Wouldn't it be better therefore for me to be seen as having laid the firm foundations of evidence for the transformation of species on which your Mr Darwin was to build? I argued the case for evolution with all the powerful skeptics of my day. The highly influential Georges Cuvier [DN: see note 3] ridiculed me mercilessly, even to the extent of gloating over my body in its pauper's grave. The so-called eulogy that he delivered on my death was described by your distinguished evolutionary theorist, Mr Stephen Jay Gould, as 'one of the most deprecatory and chillingly partisan biographies I have ever read.'

The fact is that I was reviled and died desperately poor (for which my family had to pay a heavy price) precisely because I had established the truth of, and argued strongly for, the idea of evolution. In this year of 2009, when you are rightly celebrating the bicentenary of Mr Darwin's birth, it would be nice if people might pause a little and recognize that it is also the bicentenary of my main work, *Philosophie Zoologique*. [DN: see note 4]

Veuillez accepter, cher Monsieur l'éditeur, l'expression de mes sentiments les plus distingués,

Jean-Baptiste Pierre Antoine de Monet, Chevalier de la Marck

Notes by Denis Noble

1. In his introduction to Harvard's republication in 1964 of *The Origin of Species*, Ernst Mayr wrote (pp. xxv–xxvi) "Curiously few evolutionists have noted that, in addition to natural selection, Darwin admits use and disuse as an important evolutionary mechanism. In this he is perfectly clear. For instance,... on page 137 he says that the reduced size of the eyes in moles and other burrowing mammals is 'probably due to gradual reduction from disuse, but aided perhaps by natural selection'. In the case of cave animals, when speaking of the loss of eyes he says, 'I attribute their loss wholly to disuse' (p. 137). On page 455 he begins unequivocally, 'At whatever period of life disuse or selection reduces an organ...' The importance he gives to use or disuse is indicated by the frequency with which he invokes this agent of evolution in the Origin. I find references on pages 11, 43, 134, 135, 136, 137, 447, 454, 455, 472, 479, and 480."

2. See Gabriel Dover's book *Dear Mr. Darwin: Letters on the Evolution of Life and Human Nature* (Phoenix books, 2001).

3. Cuvier argued that the fossil record showed sudden, not gradual, changes – an idea that Stephen Jay Gould later espoused in his theory of punctuated equilibrium. Despite the similarity of his ideas with those of Cuvier, he was shocked by the dismissive tone of Cuvier's 'eulogy' of Lamarck.

4. *Philosophie Zoologique* is a much better book than one might imagine, given the low esteem in which Lamarck is held today. He really did establish the transformation of species and, although he was not the first to develop the idea of evolution, he was an indefatigable proponent of the idea at a time when it was even more ridiculed than in Darwin's day – recall that Lamarck died (1829) long before publication of *The Origin of Species* (1859).

John Zachary Young – invitation to the dance

Andrew Packard (left) and Fabio DeSio

"*Thus there is, in most of JZ's scientific design and output, a tension between his desire to investigate integrative functions of organs and systems as a whole and the practical constraint that to do this requires the reduction of a system to an experimentally manageable and interpretable entity*"

Memoirs of Fellows of the Royal Society (Boycott, 1998)

That a zoologist and former professor of Anatomy at University College is a natural for a 'Memorable physiologist' article may be glimpsed from a figure illustrating James Oschman's '*Energy Medicine*' (Oschman, 2000) (Fig. 1) taken from JZ Young's *Life of Mammals*, 1957.

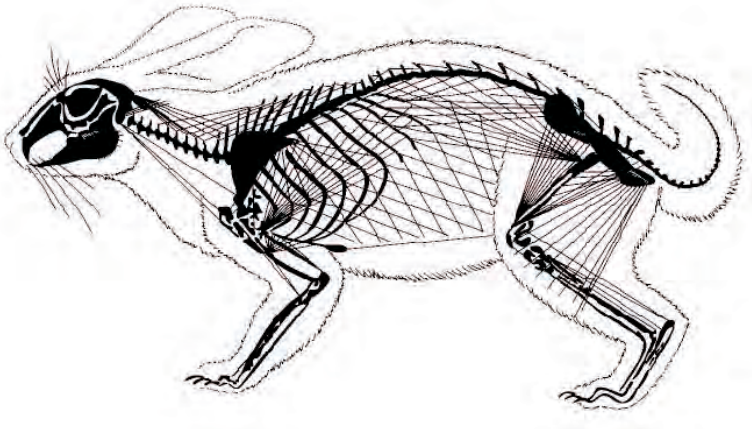


Figure 1

Despite having become head of an anatomy department in a medical school, Young always considered himself a biologist, and deliberately tried to pour biological wisdom into the mechanical art of dissecting bodies and naming their parts. His contribution to physiology is by no means limited to recognizing the importance of the giant fibre system of squids, nor to his happy facility for grafting germinal ideas from other fields into his own. Perhaps the chief 'value added' of an abundant working life is his continuous, and largely successful, insistence on always keeping the whole in mind: a characteristic he shared with Sir Charles Sherrington.

A difficult balancing act. Often it took the form of asking questions that he could not answer. In a way, this is also true of the figure of the rabbit.

Young was elected a Member of The Physiological Society in 1932 (then to Honorary membership in 1978). Who was the proposer we wonder of this 25-year-old demonstrator in comparative anatomy in whom many influences combined? He had not long returned from occupancy of the Oxford 'table' at the Naples Zoological Station – start of a trail that led to the squid giant axon rediscovery. He was part of a circle that included Sherrington whose young co-workers (Denny Brown, then a Rhodes Scholar, being one) were introducing new techniques into neurophysiology (see Boycott, 1998). He put a fondness for drawing – part of the training in zoology at the time – to very good use. Indeed, one has the impression that the seed of the later success of giant axons with biophysicists lay as much in his bold portrayal of the system as in the anatomical investigations that led to it. The emotional engagement of the scientist in his balancing act between the details and the whole – the tension of which Boycott writes – is to be found in the drawings. The 'JZY' is always tiny: almost *microscopic* at the posterior tip of the mantle in the much-copied version of 1939 (Fig. 2), same year as the first Hodgkin and Huxley intracellular recordings! Was it modesty, or awe, before the richness uncovered?

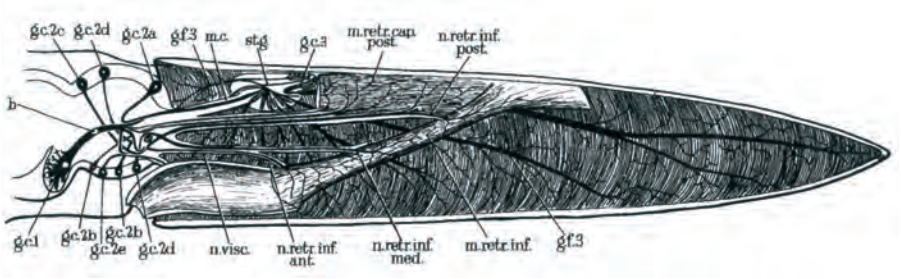


Figure 2

Drawing always drawing. Saturday mornings in London were devoted to the microscope: notably to serial sections of whole brains incubated in silver and embedded in paraffin, cut just thick enough to follow main connectives as well as the orientated receptive fields of single neurones – notably of the octopus.

The original of the rabbit in *Life of Mammals* (see Fig. 3) has every skeletal muscle–tendon unit numbered and named, represented only as a straight line between origin and insertion. Whatever the specific intention behind all the effort involved, Young was evidently after something that would convey the dynamic and integrated nature of the body. Sadly, neither of the artists in his department at the time, Miss ER Turlington and Miss JID de Vere, is alive to relate its turbulent history. The accompanying text in chapter 8 concerns the mechanical forces acting through the arrangement of struts and ties as the animal moves which

"*should be at every point proportional to the bending moments ... even more*

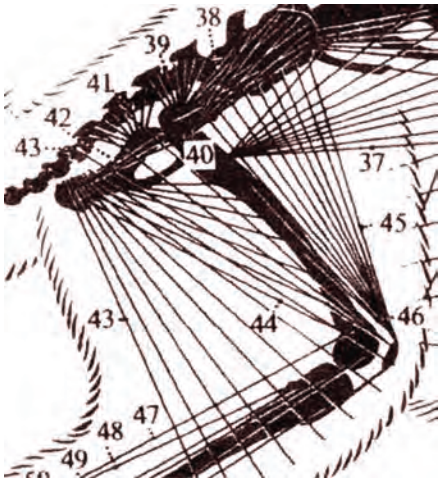


Figure 3

clearly in those hoofed mammals that are large and rapidly moving"

followed rather lamely by

"*There is a danger that such comparisons may be accepted uncritically ... they give only suggestions and not exact solutions of the statics, still less of the dynamics of the vertebrate body*".

Banal as this instance of Young pulling himself up short before the unanswered questions may seem, it is also an invitation to the dance: an act of complicity with the student.

Oschman shows us where the dance can lead. Duly disregarding the numbering on the original, he sees it as a beautiful "*tensegrous*" network.

The hard science of tensegrity has been in the literature for quite a long time. So have the findings which see it extending through the collagenous fascia of the body as a liquid crystalline continuum responsive to a range of physical forces over a range of dimensions (see Ho *et al*. 2006). Even if John Young would have been out of his depth in assessing the relation of these forces to molecular structure, and agnostic about its role in therapeutics, he would have been pleased to see the figure used to promote this ultimately simple idea, and excited by the possibility that proton conduction through the tensegrity system integrates the body. It would have coincided with a life-long interest in communication theory and memory. The pity is that, while inter-disciplinary endeavours have long become the norm in biological gatherings, there seem to be few figures ready to make the bolder leap: to use their scientific stature to embrace the implications of such 'fringe' ideas and work on their incorporation into the mainstream[1].

Young was too much a rationalist[2] to wish to be called a holist.

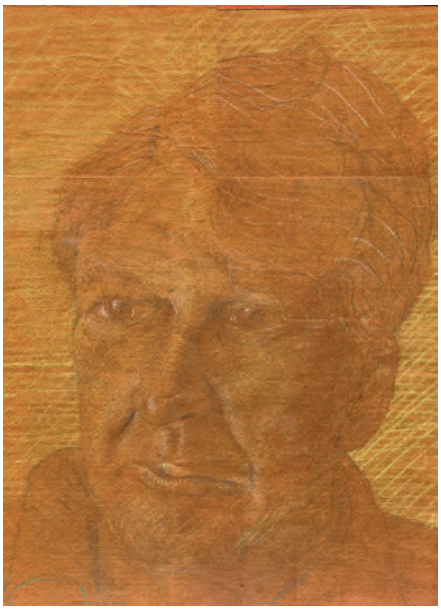
"*Addiction to holistic concepts ... an occupational disease of neuroscientists ... and of psychologists ... is a curable disease from which one recovers by patient therapy with microscopy, microanalysis or microelectrodes*" (Young, 1975).

Nor would he have wished to be tarred by association with Jakob von Uexküll. Yet he and the father of *Umweltforschung* – author of '*Umwelt und Innenwelt*', who is having something of a renaissance amongst semioticians at the present time – had some surprising things in common: professional interest in cephalopods, surgical intervention and functional anatomy of the octopus brain. Most intimately of all, both loved Naples, and this was reciprocated. von Uexküll records the remark of a Neapolitan (anxious to make him feel one of them) that he was not a foreigner but a local (Il signore non è un forestiere, il signore è di qua). JZ went one better being awarded honorary citizenship (see left) in 1991 for his long association with the city.

Both Uexküll and Young needed to draw general and philosophical conclusions from their experiments and with it the sense of a duty to communicate these thoughts to others. For the historian, their pursuit of this 'noblesse oblige' is no trivial issue. Both biologists took up the task of making scientific knowledge valuable and available to the widest possible audience. Although both of them engaged seriously with what we now call popularization, their principal targets were their respective scientific communities. They were concerned with the elaboration of a new, improved scientific terminology, a way of naming things and their relations that allowed a steadier


L'Amministrazione Comunale
di Napoli
Delibera
conferire la cittadinanza onoraria
della Città di Napoli al biologo
Prof. John Zacchary Young
quale pubblico riconoscimento per la
saggezza e l'umanità tipiche delle mi-
gliori tradizioni napoletane che hanno
caratterizzato la Sua lunga permanenza
a Napoli ed improntato tutto il Suo lavoro
di insigne scienziato, contribuendo all'ar-
ricchimento del patrimonio culturale del-
la Stazione Zoologica e della Città intera
(Deliberazione n°357 del 9-9-1991)
Napoli, 8 ottobre 1991
Il Sindaco

Deliberation of the Naples City Council conferring Honorary Citizenship on JZ Young – 8/10/1991. 'per la sagezza e l'umanità tipiche delle migliore tradizioni napoletane' (for wisdom and humanity typical of the best Neapolitan traditions).



JZ Young in 1966 – from a pencil and crayon sketch on brown paper by Andrew Packard.

progress in the sciences: pointing at "*what to look for, and where*" (Young, 1965).

As a consequence of their strong opinions on the place and role of biology, both Uexküll and Young grew very critical of modern physiological language concerned with chains of causal relations and with 'mechanical running'. Young's opposition to the narrow aims of physiological reductionism (concentrating on the cell as the proper way to address living phenomena) was that it diverted valuable scientists from the bigger and more important questions. Commenting on Hodgkin and Huxley's Nobel Prize in Physiology or Medicine – officially 'for their discoveries of ionic mechanisms involved in the nerve cell membrane' – he once half-jokingly said: "*To be unkind, one might say it was like giving a Nobel Prize for Literature to people who had advanced knowledge of typewriters, of ink, or perhaps of radio transmission*" (Young, 1977).

Both scientist/philosopher insisted on the relationship between organism and environment; Uexküll devoted much labour to the reform of biological language, coining a number of words (such as *Innenwelt*, *Umwelt*, *Funktionskreis*), which gained a vast popularity and haunted generations of translators! Young, from quite different origins fostered in the thinking of Darwin, wrote of the brain in terms of coding, information and programs, etc. gleaned from his association with the pioneers of cybernetics.

In their emphasis on communication as a key to interpreting human existence and life in general, both Uexküll and Young came close to present day bio-semioticians (Kull, 2001). Their main point of convergence is the importance of interpretation and meaning for life itself and, subordinately, for the science of life. For Uexkhüll it was a matter of "conformity to the plan", of meaning, of "biological value" rather than "physiological role" (von Uexküll & Kriszat, 1934). Ironically, it is probably easier for contemporary physiologists to accept Young's almost Whiteheadian statement that

"l*iving systems can properly be said to act in pursuit of certain aims. Each tries to achieve certain standards appropriate to its way of life. The result of this continual striving, choosing and deciding, through millions of years, has been a progressive accumulation of information about how best to live*" (Young, 1978)

than it is for contemporary evolutionary biologists versed in the mathematics of selection theory.

This awareness of the importance of language – interpretation and meaning – was expressed in very different ways by the two. Uexküll's main aim was to make biology a proper and independent science, by defining its object against that of the physical sciences. Young sought to improve science in general and, more widely, the understanding and power of mankind by refining its language in order to cope adequately with the most important, and most complex, aspects of life.

All of which may seem far removed from anatomical description of every known kind of statocyst amongst squids and octopuses which occupied much of his retirement in the Wellcome Institute of the History of Medicine, and from the 53 named skeletal muscles of the rabbit fitted in to the regimented routine of his heyday in Gower Street.

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[1]One of the pioneers of *conduction in the liquid crystalline continuum* (David Knight, personal communication) has supplied us with this example of such global approach:

"If injured or ischaemic tissue becomes more acidic, information about this could be conducted, analysed and acted on by the continuum".

[2]Young's lucid account "*Why I am a rationalist*" for the Rationalist Society, aged 80, is not listed in bibliographies.

AV Hill (1910)

The possible effects of the aggregation of the molecules of hæmoglobin on its dissociation curves

J Physiol **40** (Suppl), iv–vii

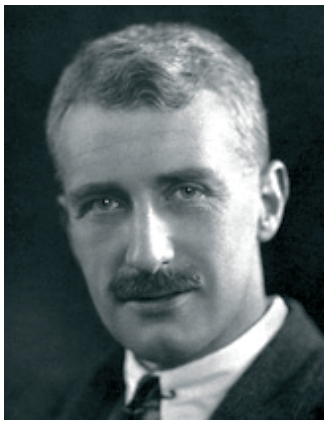
This time our look in the Archives turns to the *Proceedings* part of *The Journal of Physiology*, and a meeting of The Society that took place at King's College London on January 22nd 1910. The meeting marks the first one attended, and first communication to The Society – one of only three at the meeting! – of AV Hill (1886–1977), Nobel Laureate, doyen of British biophysicists, and giant of 20th century physiology.

Hill (christened Archibald Vivian, though he disliked both names and was always known as 'AV') was just twenty-three at the time. He was working in the Cambridge Physiological Laboratory, having taken his Physiology degree final exams there the previous summer (1909) and his Mathematics finals two years earlier. He had published one single paper, the previous month (Dec 1909) in *The Journal*. He was not yet a member of The Society (he was not elected until two years later, in 1912) and was introduced for the King's meeting by his friend Joseph Barcroft.

Hill's main scientific interest through his career, and the one that was to earn him the Nobel prize, was heat production in muscle, and muscle energetics and contraction. However, his earliest work on a number of diverse problems foreshadowed one of his wider contributions, the bringing of mathematics and quantitative thinking to physiology. Hill's protégé Bernard Katz describes this in his *Oxford Dictionary of National Biography* entry on Hill:

"[Hill's] first published papers were concerned mainly with a theoretical and quantitative analysis of experimental results obtained by himself and his senior colleagues in the Cambridge laboratory. They included an analysis of drug action in muscle tissue, of the reaction between oxygen and haemoglobin, and of the effects of electric stimuli on nerves. Although Hill later regarded this work as being of little importance, it contained the first mathematical formulation of drug kinetics later generally known as the Michaelis–Menten or Langmuir equation. It also introduced the concept of co-operativity in complex chemical reactions, signified by a quantity which was widely referred to as the Hill coefficient."

David Colquhoun, in an interesting article on the origins of quantitative



approaches to drug–receptor interactions, gives a nice account of Hill's December 1909 paper, which derived the Langmuir adsorption equation some ten years before Langmuir, and the January 1910 communication.

Hill derived the equations that would govern a reversible association between haemoglobin and a ligand, and compared these to the experimental oxygen dissociation curves measured by Barcroft and others. Hill sets out what would subsequently be known as the Hill equation, describing the fraction of the macromolecule saturated by ligand as a function of the ligand concentration. Hill's equations also took into account possible self-association (multimerization, as we would now say) of haemoglobin. The resulting successive ligand (oxygen) binding events to multiple haemoglobin units give rise to what would eventually become known as the Hill coefficient.

Colquhoun notes that Hill (presciently?) did not attempt to ascribe precise physical meanings to the parameters in his equation:

"My object was rather to see whether an equation of this type can satisfy all the observations, than to base any direct physical meaning on [the parameters]".

Colquhoun drily adds: "His caveat has often been forgotten since then."

Speaking many years later (Hill, 1969) about how he had come to take up physiology, Hill said:

"A short answer... is, because Walter Morley Fletcher was my tutor at Trinity [College]...During my first year [at Cambridge] I began to lose interest in some of the things [in mathematics] that to me seemed rather remote from reality and hankered after something more practical. I realize now that I was much better fitted to engineering than to mathematics, but physiology proved in the end to be much like engineering, being based on the same ideas of function and design."

Fletcher persuaded Hill to complete his Mathematics degree before pursuing new directions. As Hill tells us:

"In 1907 I took the Mathematical Tripos, which in those days was an extraordinary business, with fourteen three-hour papers and great public interest as to who would be Senior Wrangler [i.e. achieve the top mark of the year]. It was too much like the Grand National with all its obstacles. I did quite respectably in fact, but nobody encouraged me to go on with it; which was a very good thing. So I sought Fletcher's advice again, and decided soon to become a physiologist."

In the summer of 1910 Hill published the first instalment of his scientific life's work on muscle energetics (Hill, 1910). This work was to culminate in the Nobel Prize in 1923 – though 'culminate' is perhaps the wrong word, given that Hill continued to publish papers on muscle energetics in *The Journal* until the early 1960s (the last ones, in 1961 and 1962, with his final PhD student Roger Woledge).

Though Hill is often associated with UCL, the institution where he spent all his later career (after 1923), the Nobel Committee honoured him for his muscle work carried out in Cambridge (1909–19) and Manchester (1920–23). During the Manchester years Hill, who had been a keen athlete, developed a parallel interest in human exercise physiology, and is credited with originating the idea of 'oxygen debt'.

Hill married into the Keynes academic dynasty (his wife Margaret was the sister of the economist John Maynard Keynes, and aunt to Professor Richard Keynes). Among Hill's four children, his son David or 'DK' Hill (1915–2002) followed in his father's footsteps to become a muscle physiologist, Professor and FRS. Nicholas Humphrey, Hill's grandson, has written a touching memoir of helping his grandfather with his experiments as a child in the early 1960s in a chapter of the book *Curious Minds: How a Child Becomes a Scientist.*

AV Hill was an early example of a scientist who engaged in many spheres beyond the laboratory, and it would take a decent-sized book to do justice to even a selection of his activities. He worked in wartime 'operational' research in both World Wars, and was an independent MP for Cambridge during the Second War. He served The Physiological Society and Royal Society in many capacities, and was an early populariser of science,

giving the 1926 Royal Institution Christmas Lectures. Perhaps the 'extra-curricular' activity for which he is most remembered is his leading role in the 1930s in the Academic Assistance Council (AAC) which helped Jewish academics flee from the Nazis.

Hill had used his Thomas Huxley Memorial lecture in November 1933 to denounce the Nazi persecution of the Jewish people, especially of scientists who had been forced out of Germany. This triggered an extended argument, in the pages of *Nature* in early 1934, with the German physics Nobelist Johannes Stark who had become an enthusiastic Nazi. Stark insisted that Jews were not being persecuted, only people guilty of "high treason" against the Nazi state. Hill's response was withering:

"With Prof. Stark's political anti-Semitism I need not deal... it appears absurd. It is a fact, in spite of what he says, that many Jews or part-Jews have been dismissed from their posts in universities ... No doubt in Germany, after this reply, my works in the *Journal of Physiology* and elsewhere will be burned."

The correspondence famously ended with Hill commenting, with characteristic dry wit, that since his previous letter he had received many donations to help the AAC's cause – but he felt he could not really take the credit, as the donors' generosity surely owed something to Stark's (racist-ideological) arguments. Bernard Katz, himself a Jewish refugee from the Nazis, sought Hill out partly because of the correspondence, and would later write that the letters "gave me the first glimpse of A.V. Hill's personality...[which] I found... so attractive that I made every effort to go and work with him".

Katz also quoted a favourite saying of Hill's: "Laughter is the best detergent of nonsense".

The definitive scientific biographical source on Hill is Bernard Katz's monumental Royal Society Biographical Memoir; for a shorter introduction Katz's *DNB* entry is a useful starting point.

Austin Elliott

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Electronic interference

Here is an entry from my diary from some time last Autumn. I am willing to bet that almost every academic scientist has multiple similar tales.

Day trip to London for meeting.

On returning home, log on to email to check what has shown up in the nine hours since I last logged on early that morning (and sent a few urgent messages) prior to toddling off to catch the train. (I opted not to pay Virgin Trains ten quid for the privilege of wireless internet access on the train so that I could actually get some reading done for a change. And I refuse to buy an iPhone).

A delightful **twenty-one (21)** emails await my perusal.

To be precise:

Three (3) pieces of junk email from suppliers and biochemical and molecular biology reagents

One (1) junk email offering to put me in a directory of important people

One (1) junk email from the Univ, sorry, one 'In-house University communications bulletin'

One (1) depressed/depressing bulletin from the staff trade union

Two (2) inconsequential Faculty announcements

One (1) notice about a staff meeting (2 hours minimum duration, judging from experience) that I will avoid if at all possible

One (1) email correcting incorrect date of said staff meeting

Two (2) emails about research seminars I probably won't have time to go to

One (1) email about a journal editorial meeting next year that I probably won't go to as I will be teaching that day.

One (1) email telling me about Faculty quota PhD studentships that I won't be able to recruit any students for – even if I were high enough up the priority ranking – as I don't have enough research grant income to 'cross-subsidise' a 3-year PhD project

One (1) notice about a colleague's retirement do – lucky b*stard.

Unfortunately I am teaching when it starts and I suspect they will have drunk all the free booze by the time I get there

One (1) email from the Senior Secretary explaining that we (a research group of about 20 academics and associated staff) will now have secretarial support from a single secretary for two hours/week (that's for all of us – and before you tell me that is a bit thin, it was previously no hours/week, so things are looking up)

One (1) email from the Faculty Disability Support Officer telling me: (i) I have no students with severe disabilities that would mandate special educational provision; and (ii) I have one student in a tutorial group this year who has a disability, but not a disability that will require me to do anything beyond 'normal academic practice'. So... that looks like an email telling me at some length that I don't have to do anything different from what I always do. On the whole that is a plus, though I'm not sure why it meant I needed to be sent the email

One (1) email from a colleague reminding me to upload my lecture next month to the relevant E-Learning website (or is it a portal?) 'assuming the Faculty who we do this teaching for have granted you all access to their site – we're not sure yet'

One (1) email with actual useful information from a colleague about an ex-student I am writing a reference for

And last but not least:

Two (2) automated emails from the Faculty email server **telling me I have too much stored email.**

sigh

Sometimes you really have to wonder what universities did in the days before email. How on earth did anything ever get done...?

Mark Cain

Society of Biology – the first months

As most readers will be aware, the Society of Biology formally came into existence on 1 October 2009 following the unification of the Biosciences Federation and the Institute of Biology. Although we plan to build on the heritage of these two important bodies, it is important for all of us to see the Society as a new organisation with a different outlook and approach to its organisational parents. For the first time we have one body to represent the interests of all biologists in the UK, creating a single powerful voice to advise and inform Governments and make a difference. That aspiration can only be realised if we are a nimble organisation, quick to respond to opportunities, capable of learning from our mistakes and willing to work in partnership. We also need to be truly proactive to really drive the policy agenda.

At the time of reading this article we will be less than six months old and there will still be plenty of opportunity to shape the way we work. But, to do that we need to understand what matters to our members, how you will judge if we are delivering for you and how best to involve you. Any member of the team here would be delighted to hear your thoughts and, as the newest recruit, I am particularly keen to learn about the way The Physiological Society would like to be represented by us.

The Society of Biology is a single unified voice for biology:

- advising Government and influencing policy;
- advancing education and professional development;
- supporting our members;
- and engaging and encouraging public interest in the life sciences.

The Society now has over 70 Organisational Members and nearly 12 000 individual members. This represents 80 000 biologists, giving us the legitimacy to speak with authority in all our work.

Our Council has identified four priority areas for 2010:

Firstly, **practical biology.** No matter which biological discipline undergraduates or postgraduates follow there needs to be the opportunity to practise science at the bench or in the field. It is simply not tenable to expand undergraduate science education without additional resource to facilitate hands-on experience of designing real experiments and interpreting the results. As Keith Gull, Professor of Molecular Biology at Oxford University and Council member of the Society of Biology, said in a recent interview to the *Standard*, responding to Lord Mandelson's announcement on spending cuts, 'A perfect storm is gathering. Our next generation of scientists will need to look very carefully at the quality of degrees on offer. If we want top scientists – to innovate, to find out fundamental truths and to get us out of recession – this is simply not good enough' (sic). There has to be the resource to properly fund practical biology both in schools and in the higher education sector. We will be pushing this message at every opportunity, especially in the run up to the election.

Secondly, the **impact of biology**, a central theme in the recent consultation on the Research Excellence Framework. Most biologists accept that the public have a right to know that the money they spend on research is being spent wisely. Its impact on our economy, health care system, environment and society is important to recognise. But it has to be a sophisticated measurement. We plan to build on existing work and present a consistent and clear case around the impact of biology from blue sky research to the most applied. Case studies will be an important part of that and physiology is surely one of the best sources. If you have data or views to share please email me at markdowns@societyofbiology.org

Thirdly, we will continue to work on a pilot **accreditation programme** to report back to the Office for Life Sciences. The Government has asked us to look at ways in which some biological science degrees can be accredited to give greater confidence to students and employers that they provide the solid grounding needed for employment. There is no doubt that the topic arouses strong views. The academic community doesn't want to be forced into a corner with no room for innovation in their degree programmes or to become a surrogate for technical training programmes, whilst industry bemoans the lack of hands-on laboratory skills of many graduates. I am convinced there is a route to delivery of a solution that meets the needs of both camps. A lot rests with the terminology used. Any accreditation programme we take forward will benefit from wider consultation and will certainly not be compulsory. It is likely to focus on core requirements for biological science courses to be accredited, such as numerical content, experimental design, opportunity for hands-on experimentation and intellectual rigour. It is certainly not about accrediting individuals or asking for coverage of specific training tasks or a defined list of techniques. For sure, biology is more diverse than chemistry or engineering, but by starting in specific areas real benefit can accrue, along with experience. To find out more visit www.societyofbiology.org

Mark Downs

Finally, we will of course be talking to all the parties in the run up to the **General Election**, forcing them to focus on their science agenda and representing the interests of biology, raising its profile and using our work on 'impact' to argue for investment.

The Society will also be working on many wider education, science policy and public understanding of science issues and, of course, trying to evolve new services to benefit our members. We welcome your suggestions for the Society.

Mark Downs

Chief Executive, Society of Biology

(see also article on accreditation on p. 38)

Should The Physiological Society accredit university courses?

In the good old days when I were a lad, studying science meant doing proper experiments. Chemistry classes at school involved concentrated acids, blowing down Bunsen burner gas tubes, occasional explosions and lots of colourful reactions. Most of my friends continued this experience at home and made their own fireworks, constructed illegal stills, became amateur glassblowers etc. In biology, we cut sections (using razor blades) and viewed them under microscopes. We dissected hearts, eyes and even a dogfish and a rat. On to university we budding scientists went, where the practical experience continued. Every afternoon we were in the lab stimulating frog muscles, contracting pieces of ileum, dissecting locusts, examining the behaviour of flatworms and so on. We even had practical exams which you had to pass to get through part one of finals! All the students had to do a final year practical project (followed by a viva) and I spent many hours trying (and eventually succeeding) to measure after-potentials from rabbit superior cervical ganglion and investigating whether they were adrenergic or cholinergic. My fellow students and I went out into the world with a background of lab work and a pretty clear idea of whether we wanted to do more of it or whether we wanted to avoid it for evermore. In fact, most of my friends did go on to become real scientists working in academic, health service and industry labs.

So what has changed? Well, for one thing, the emergence of the dreaded health and safety police. We all accept that it's important to conduct experiments safely, but today's society seems to regard risk as a 'no go' area. If you take no risks then life would be tediously boring and nothing would ever change. OK, some experiments do involve a degree of risk, but isn't learning how to manage risk a part of education? My personal experience is that riding my bike is a lot more risky than any lab work I have ever done (and I have the scars to prove it!). So, if health and safety stops practical science at the school level, what happens these days at universities? Well, in addition to H+S, there is the big problem with money for practicals – there isn't enough of it. Government policy has been to increase the number of kids going to university but it has actively reduced the resources needed to teach them properly (practical subjects now get less supplement over classroom subjects than they did). As a result, the practical aspects of science in most physiology and other bioscience courses have diminished greatly. Few students do a meaningful final year practical project and practical exams are a forgotten memory. Of course there are always library projects which equip you just as well for a life in science (don't they?).

So what are the implications of our risk-aversive society and of a government that encourages more kids to go to university without providing adequate resources to teach them? You probably already know, the modern bioscience graduate, although just as intelligent as their forbears and with probably a wider theoretical training, cannot work in a lab without additional training. They also have little idea whether they want to do real practical science, because they have no experience of it. Little wonder that we now have 4 year PhDs, in which the first is a lab-training year – or that employers won't consider new graduates for scientific roles unless they have done a masters with significant practical components or had an extramural year in industry. In fact, many industry employers are recruiting PhDs to do what were previously regarded as graduate jobs. The other worrying feature of our current 'science training' is that industry is outsourcing increasingly more of its research to India and the Far East, where graduates do get a solid lab training. One of my ex-colleagues from Pfizer has had his job changed from 'Recruitment Manager' to 'Outsourcing Manager' – get the picture?

So is there anything that can be done, or do we just accept that scientific training in the UK is inevitably downgrading and that long term we don't need graduates who know how to design and perform experiments? The Office of Life Sciences, set up by Gordon Brown in January 2009, doesn't think so. In its recent 'Blueprint' document (see http://tinyurl.com/n44ema) it highlighted the lack of practical skills and high level maths in current undergraduate bioscience courses, and the implications of this for UK bioscience. (Now I don't claim to be any great shakes at maths, but I did come out of school knowing about logarithms and making serial dilutions, and from university with some knowledge of statistical analysis and which test to apply and when.)

The Office for Life Sciences has proposed that one thing that might help improve training is accreditation for university courses that provide a solid practical training and maths at an appropriate level. Jeremy Ward, Max Headley and I recently attended a Society of Biology workshop on this very topic. The workshop revolved around the proposal that the SoB would manage an accreditation process for bioscience courses that would concentrate on the level and quality of practical training and maths that the courses provide (see also p. 32). Member societies, such as The Physiological Society, would provide the expert assessors for the accreditation process. The attendees at the meeting were from a number of universities (predominantly the newer ones) and included molecular biologists, plant biologists, geneticists, physiologists and pharmacologists. We worked in groups and discussed how accreditation might work. It quickly became apparent that the flaw in the accreditation idea is that whilst most HEIs would like to provide more lab training, they can't afford it. So, most of us concluded pretty fast that any accreditation system had to be linked to an increase in

HEFCE funding. SoB will be meeting with HEFCE to discuss this issue and let's hope they get this message across clearly and forcibly. Some people at the meeting wanted a stick as well as a funding carrot to give accreditation 'teeth', although it wasn't clear what this would be, apart from potential students voting with their feet. Worryingly, a significant number of the academics present appeared not to see the need for students to gather data from their own experiments but thought that analysis of existing data was sufficient training for a scientist. It was also pointed out that only a small percentage of science graduates go on to do real science, the majority using their degree as a stepping stone into other careers that may or may not be science related. A further important consideration was whether the 'elite' universities would be bothered whether their courses were accredited or not, which reinforces the necessity of backing accreditation up with extra resources.

So is there a viable answer to the problem that we are not providing an adequate training in practical lab skills and maths for our science graduates? One suggestion (which I first heard from Max Headley) is that there should be an MSci option to science degrees that would involve a 4th year. The extra year would provide the practical lab experience and mathematics that would equip its students for a scientific career and a prerequisite of this approach was that this should be funded at an appropriate level. Only a small proportion of the more able science students would take this option, principally those who are interested in going on to a PhD and those who want to pursue a lab-based science career. This seems to me to be the most feasible option, given the negligible chances that Government will provide sufficient funding for a proper scientific training for all science students. Of course, this still requires additional HEFCE funding, but accreditation would then be worthwhile and could be a requirement to receive the extra funds. We could then start producing science graduates who are attractive employees for industry and government labs and research students who 'hit the ground running' in academia. It strikes me that both the students and the UK science base would benefit. But maybe I'm just a grumpy and deluded old physiologist.

Mike Collis

Royal Society Seminar – Science collaboration in a multi-polar world

21 September 2009

This seminar, chaired by Lorna Casselton FRS, had presentations from Deliang Chen, the new Executive Director of the International Council for Science (ICSU), and Alan Thorpe, the Chief Executive of the Natural Environment Research Council (NERC). Chen focussed on structures for co-operation provided by ICSU, whereas I found Thorpe's presentation particularly striking in illustrating how far the UK Research Councils had moved in supporting international links, a quite different state of affairs from when I was working in Polaris House 20 odd years ago, when they mainly seemed focused on the UK scene. Lorna emphasized an important driver for this change, in that Governments now recognize the need to promote research across international networks to stay internationally competitive, and address pressing global problems.

Chen gave the background of ICSU as a non-governmental organisation founded in 1931 with the aim of promoting international and inter-disciplinary research, links between science and science policy, and to speak for the international scientific community in UN forums. Over the next few years they aim to remain strategic, create new forums, strengthen their network of regional offices, and integrate social and natural science in tackling issues of international concern. This approach had led to some remarkable successes in the past, e.g. the international Antarctic Treaty in the 1960s. This in turn led to monitoring of the ozone hole and the Montreal Protocol for tackling its underlying causes from pollution.

Alan Thorpe emphasized that international collaboration is now seen as being of vital importance by the UK Research Councils. The aims are to promote: UK collaboration with, and access to, the best foreign research; the global movement of researchers; influencing international research agendas; the UK as a world centre for research and innovation; and tackling global social, environmental and other challenges. Unsurprisingly they have a special focus on Europe and the European Research Area. The impact of the international strategy is being felt in the growth of international co-authorship, the UK being seen as the partner of choice in US collaborations, and the high success rates of applications to European Framework Programmes. Research Councils UK (RCUK) has now set up offices in key countries, UK Research Offices (UKROs) in Brussels, Washington, China and India, in order to help UK researchers design and get funding for collaborative programmes (e.g. a focus on synthetic biology with the National Science Foundation, and MRC's active collaboration with various foreign agencies on the Global Alliance for Chronic Disease). There are Memorandums of Understanding with various countries, and NERC has a very strong relationship with ICSU on e.g. the Inter-Governmental Panel on Climate Change.

There was much support for the concept of promoting international space beyond nation state boundaries, but it was felt that, with too many international organizations involved, there were problems in co-ordinating programmes, creating effective structures and setting priorities. In particular, the UN, UNESCO etc. are too slow and consensus driven to have much effect. The lead is often better taken

by less bureaucratic organizations, and organizations with a clearer remit and focus such as the Research Councils.

Liz Bell

Royal Society Policy Lab – The future in your brain

24 November 2009

This was a thought-provoking debate on some of the social, legal and ethical issues posed by developments in neuroscience, with presentations from Steven Rose (Professor of Biology and Director of the Brain and Behaviour Research Group at the Open University) and Sarah-Jayne Blakemore (Leader of the Developmental Cognitive Neuroscience Group at UCL). The audience was more diverse than the usual mix of scientists, politicians and civil servants, and included people from HM Revenue and Customs, the Financial Services Authority, and the Serious Organised Crime Agency. I was amused to note none of them was forthcoming about their interests in the Q&A session at the end!

Steven highlighted many radical advances in neuroscience that were exciting scientists, philosophers, health care professionals and even the military with its promises of being able to eventually explain, mend and manipulate the mind. He described the following major 'promises' coming from neuroscience research:

- New drugs and other treatments to restore function, treat neuro-degenerative diseases, and to protect against the development of disease in people identified as being at risk are unlikely to be controversial, even if this involves human–machine interfaces. However, if implants/drugs etc. are then used to enhance the faculties of healthy individuals, a whole can of worms starts to be opened up. A good example is the development of cognitive enhancers to treat Alzheimer's; these might end up being used by people who want to enhance their otherwise normal cognitive functions in an analogous fashion to how some athletes misuse steroids.
- Increased use of 'predictive' genetic testing for neurological and psychiatric disorders.
- Redefining mad and bad and how it is treated. The view that you are your brain is becoming pervasive, and has many implications in how offenders may be viewed under the law. Defending lawyers in criminal cases may be saying that it wasn't the defendant's fault, his/her brain/genes made them do it. Should people be criminalized for conditions they might not be able to help? Much more thinking needs to be done as to how neuroscience evidence should be handled in legal contexts. In terms of handling anti-social behaviour, we are already seeing evidence of problems in the over-diagnosis of attention-deficit hyperactivity disorder, with giving children powerful prescription drugs being seen as the norm.
- Even more worrying is the potential use of neuroscience for security surveillance and military purposes. One company in the USA openly claims that their brain fingerprinting techniques can identify people with terrorist thoughts and training, and even though there is not much evidence that it works, it has already been used in some US courts. The military have been putting a lot of research money into e.g. the development of new psychoactive chemical weapons such as calmatives, and transcranial magnetic stimulation technologies to directly affect people's thoughts and moods.

Sarah-Jane then looked at some of the uses and misuses of neuroscience in education. A whole industry has grown up around the idea of influencing the development of young brains through the promotion of products such as Brain Gym, Baby Einstein etc. Many of these products are based on poorly understood research, or research where the results haven't been replicated, or completely off the wall pseudoscience. Parents have been targeted for such products with the idea that the critical period for such development is from 0 to 3 years old, and although this is an important phase, it ignores the fact that it was based on research in monkeys who reach sexual maturity at 3 years. The human brain continues to undergo development through to the early 20s, so good education is vital at all stages for young people, and in fact people of any age benefit from learning due to the brain's plasticity. One research project of interest to all parents of adolescents looked at the different responses of adolescents and older people to risk taking in driving simulations. The study found that although both groups were equally careful when on their own, adolescents were very influenced by negative peer pressure and indulged in more risk taking with friends. Her recommendation of 'don't let your children drive with their mates' sounds sensible. She finished with some interesting examples of good and bad explanations for cognitive effects, all of which then looked more convincing if even an oblique reference to neuroscience research was inserted. This was used to dangerous effect in some product advertisements.

The conclusion of the discussion was that overall, neuroscience has made many outstanding discoveries that have revolutionised our understanding of the brain, but this is being held back by a lack of integration across different levels of research from molecular to systems. We need to get a grip on some of the more outlandish claims being made, and seriously consider the ethical issues of possible future applications. Neuroscience is increasingly data rich, but theory hasn't developed at the same rate. Brain development, and how an individual's sense of self and consciousness come about, are still enigmas. Finally, as one discussant noted, there is still a role for good old fashioned psychology research.

Liz Bell

Gareth Roberts Science Council Lecture

20 October 2009

The keynote speaker for the lecture this year was Sir David King, formerly the Government's Chief Scientific Advisor, and now Director of the Smith School of Enterprise and the Environment at Oxford University. He gave a rousing description of some

of the key issues that the world faces, and the role of science and scientists in seeking solutions and influencing government policy.

He said that humanity had enjoyed some 12 000 years of relatively stable temperatures and sea levels, but global temperatures are now rising out of control. The good news from this is that it has probably put paid to the planet's previous periodic ice-age oscillations, but changes due to global warming could be calamitous. A major contributor to this has been the explosion in global population due to science and technology successes. Life expectancy has vastly increased, but it takes populations a couple of generations to adapt by lowering fecundity. We will need to learn how to manage a global population of billions all of whom will aspire to a high standard of living.

There are stark lessons from history where civilisations collapsed from their inability to cope with climatic change, resource over-use and over-population, and we can already see drastic changes in our own world, such as the State of Victoria in Australia, which used to be rich agricultural land and is now beset by drought. Victoria is now dependent on desalination plants, but desalination takes energy, and if this is provided by burning more carbon, you end up in a destructive circle of more climate change. Global problems, in climate change, food production, energy production, water management, minerals, management of disease and conflict, all tend to be closely inter-linked. For example, policies to use crops for bio-fuels have contributed to starvation and a catastrophic rise in food prices. Some technologies have great potential to help, for example in India where food production is now threatened by increased flooding because of climate change, GM technologies are being used to develop rice that can survive being submerged for 3 weeks. Rejection of GM technologies is something that only developed countries can afford, but we do need to recognise public concerns about it, and governments need to manage such technologies with proper regulatory systems. In international development, King particularly highlighted the needs of Africa, which desperately needs science and skills, but our International Development Committee has not addressed this. Human capital development is vital, particularly in bolstering the higher education sector.

Governments struggle to understand how to use science to protect their citizens from disaster. A classic example was the Boxing Day tsunami of 2004, where seismologists had previously produced a map predicting it, which although it couldn't say when it would happen, did show that it was inevitable. However, when the scientists concerned tried to lobby governments in the affected region to create an early warning system, they couldn't get anyone to pay them any attention, with the results that we have seen. Governments typically wait for disasters to happen and only then try to do something about it.

So what do governments need to do? They need to put a price on behaviours contributing to climate change that we want to turn off, and should quickly implement policies where reductions in carbon emissions could be achieved quite quickly such as in energy efficiency. Governments need to create proper channels of communication with scientists to help with avoidance and better management of disasters. The key to managing population growth is education, empowerment and contraception for women. A cultural paradigm shift is needed in political and business thinking to respect and actively manage the environment. Resources must not be used faster than they can be replenished. Solving these problems will require big thinking and an ability to solve problems in parallel. The good news is that this has been successfully done in some areas such as global agreements on CFCs. We need to collectively build on this to save the world!

Liz Bell

Science for Humanity Thailand water project: using scientific knowledge to alleviate poverty

Tremendous success has been achieved in the developed world in the fields of science and technology. This has increased the standard of living and the quality of life of those who are relatively well off. Yet, unfortunately, poverty still exists in many areas of the world and many of the poor are still suffering from lack of access to clean water, sufficient energy supply, education and much more. Something has to be done to reduce the gap between the success of science and the pervasive presence of poverty in the developing world.

Science for Humanity is an innovative charity founded by one of the most prominent scientists in the UK, Professor Baroness Susan Greenfield. She founded the charity together with Justin Anderson, an IT entrepreneur, and Andrew Doman, a former Director of McKinsey. Together they envisioned Science for Humanity to bring about genuine innovation in science and technology that can make a real-life difference to billions of poor people who can benefit from scientific advances.

The strategy of Science for Humanity is to conduct open-source collaboration using its membership platform (http://collaborate.scienceforhumanity.net) which is linked from their website (www.scienceforhumanity.net). Science for Humanity proactively matches up seekers and solvers, facilitates collaboration between them, and encourages information brokerage. Seekers usually come from non-governmental organizations (NGOs) and poor communities in the developing world. The solvers are those with scientific capabilities who volunteer to develop solutions to problems in poor communities. By finding solutions to problems through the voluntary work of scientists and other solvers, innovation is fostered that could make a difference to people's lives.

Science for Humanity projects are science and technology based that have the potential to improve people's well-being including reducing their burden of disease and providing them with an economic advantage. The projects range from developing a water filtration system and a low-cost shelter for disaster relief to an open source tractor for agricultural use and green charcoal to combat climate change.

For instance, under the humanitarian area of water and sanitation, Science for Humanity has launched a project called Thailand Water. This project seeks to improve the water quality supplied by a water filtering and purification system to villagers in Tha Mai Ruak, Thailand. The current problem facing these villagers is their access to clean drinking water. The only water available to them is the Phetchaburi River located near the village, which is muddy and dirty, causing the community to experience episodes of diarrhea and other water-borne diseases.

A team of students from the International School of Bangkok came together last year to construct a water filtration system to supply drinking water to the villagers. The existing water filtration system is composed of three PVC pipes containing layers of different sizes of gravel and sand, manganese, carbon and ion exchange resin that aid in removing chemicals, rust and unpleasant smells and tastes from the water. Whilst the water has passed the standard test for chemical content, further improvement is needed to improve the bacterial content by finding ways to eliminate harmful bacteria, such as *E. coli*.

Science for Humanity is currently working with scientists to identify solutions that are not only cost effective but also culturally acceptable by the community. For instance, chlorine is heavily used in Western countries to eliminate bacteria from the water; however, some communities in the Philippines are reluctant to use chlorine due to misconception and stigma. Thus, one challenge is to find mechanisms to deliver solutions that are most likely to be sustainable. A solution to this challenge could provide approximately 200 villagers with access to cleaner drinking water, reduce the spread of water-borne diseases, and allow children to go to school and adults to work.

Thailand Water is one of several Science for Humanity projects that can meet people's needs, help to alleviate poverty and contribute to sustainable development. If you would like to learn more about our existing projects or initiate a science and technology-based project that can aid people in need, please do contact me. I hope that you found this article interesting, and that you will get involved with Science for Humanity.

Anu Devi
C Uy
Science for Humanity
(ad@scienceforhumanity.net)

Ask a physiologist!

In this issue we introduce a new section in which sixth form students have been asked to pose physiological questions that are answered by physiologists (or occasionally other specialists if they are better qualified in a subject). The questions in this issue were asked by students at St David's Catholic College, Cardiff. Do you know a teenager with a burning physiological question they would like answered? Ask them to email us at magazine@physoc.org for a chance to see their question answered in print.

Patricia de Winter

Why does your stomach rumble when you are hungry? (Alison, age 17)

Professor Rod Dimaline, University of Liverpool, replies:

The rumbling sounds are known as borborygmi, and they actually emanate from the small intestine as well as the stomach. They occur when the gut muscles contract and vigorously move around the contents – food, liquid and especially gas inside the hollow organ of the gut. The gas may be present for a number of reasons such as swallowing of air during eating and drinking, from carbonated drinks, or production by gut bacteria. Many people experience borborygmi, particularly after a meal, when the gut contains the most food, liquid and gas, and when the gut muscles are actively mixing and moving the meal through the stomach and intestines. However, these sounds are usually muted by the food and liquid present.

During prolonged periods of fasting between meals, a different pattern of movement occurs in the gut known as the migrating myoelectric (or motor) complex (MMC). This consists of strong waves of contraction that start in the stomach and pass right down the gut as far as the large intestine (colon), at intervals of about 90 minutes. The purpose of the MMC is to sweep any residual food, gut secretions, bacteria and other debris down the gut towards the colon in a kind of housekeeping exercise in preparation for the next meal. The sounds made by movement of gas through the hollow gut resonate much more loudly in the absence of much food or liquid. So although the stomach can 'rumble' at any time, the sounds are much more noticeable in the absence of food, when we are likely to be hungry. The MMC pattern of activity usually ceases on ingestion of further food.

Why do I get angry over the smallest things in life? Is there an 'anger gene' or something in the brain that triggers this? (Tomas, age 19)

Professor Laurence Steinberg, Temple Univeristy, Philadelphia, USA, replies:

Anger is a normal human emotion, experienced by everyone at one time or another. Generally we feel anger when something we want is blocked by something that is out of our control.

Although it would be oversimplifying things to say that there is an 'anger gene', we know that some people are temperamentally more inclined than others to become angry, and it is likely that this predisposition is at least partly genetic. There is a trait that psychologists call 'negative affectivity' – a cumbersome term for the tendency of some people to be quicker than others to feel negative emotions (anger, anxiety, fear, sadness). There are several studies indicating that teenagers who are high in negative affectivity were similarly prone to negative emotions as early as infancy. Many scientists believe that adolescents are especially susceptible to feeling strong emotions – both positive and negative – because brain systems responsible for regulating our feelings and, more specifically, for modulating emotional reactions, are still developing at this time.

Just because a trait has a genetic component doesn't mean that it can't be modified, or even overcome. One characteristic of individuals who are frequently angry is that they are quick to interpret the innocent actions of others in negative terms. When someone accidentally bumps into them, they assume it was deliberate. When someone forgets to say hello they take it as an intentional snub. One strategy for managing anger in these sorts of situations is to pause before reaching a judgment about the other person's behaviour and see if it is possible to put it in a different, less negative, light.

Is there a way to precisely detect the age of a human body? (Maxine, age 17)

Professor John Lee, Rotheram Hospital NHS Trust, replies:

On one level, yes, more precisely than for any other organism. This is because, uniquely, you can ask a person for their date of birth, which is one of the first things that a doctor will ask, because it is vital providing a context for interpreting other symptoms and signs that the patient may have. This is important because it has allowed medical science to correlate disease processes closely with age in humans. On another level, no. As far as I'm aware there isn't anything like tree rings in people, which would allow you to date them precisely to, say, within a year. However, there are things that change as the body ages: bones get thinner, muscle bulk lessens, teeth wear and fall out, injuries accumulate, as do skin blemishes. We all notice the effects of these things on people's appearance and we are quite good at accurately eyeballing someone's age to within a decade, or even 5 years or so. Doctors tend to distinguish between chronological age – how old someone actually is – and biological age – how old they appear to be. This recognises the fact some people age more quickly than average (especially if they indulge in damaging activities such as smoking, substance misuse or excessive alcohol intake), while others with the right mix of genes age more slowly. This means that every so often we get our eyeball estimate wrong and have met older people delighted to be taken for younger than their real age!

Although there's no general method for dating people who are alive, there may be special instances. For example, it wouldn't surprise me if there's a clever physical method of identifying the signature of the Chernobyl nuclear accident in people's tissues, and perhaps even more accurately in those who were undergoing their pubertal growth spurt at the time.

Once people have died, we lose a lot of the clues that allow us to guess someone's age. Carbon dating means that we can tell quite accurately how long ago a person died. Analysis of tooth wear can provide information, but requires assumptions about the diet. Archaeological or forensic estimates of adult age based on bones tend to be rather vague – young, middle aged and old being about the level of it. Anyone who can devise a method of accurately assessing a dead person's chronological age from their bones will open up a whole new area of research.

Questions coming in the next issue:

Why do humans need to sleep?

Why have humans lost body hair, as opposed to keeping it as a method of keeping warm?

Where and how is memory stored?

Physiology core curriculum

Some 18 months ago The Society's External Relations Committee asked me to assemble a core curriculum for the teaching of physiology. The motivation for undertaking this arose from disquiet over the closure (or merging with other disciplines) of physiology departments around the UK. An Education Special Interest Group (SIG) session held at the Cambridge meeting in 2008 confirmed that the members of the External Relations Committee were not alone in this concern. The profile of physiology as a discipline has undeniably diminished in recent years. I keyed 'Department of Physiology' into Google and found only one (unmerged) in England on the first page (Liverpool). The uncharitable might suggest that merging university departments is tantamount to taking the position that 'now we have SatNav we no longer need to maintain our road system because if one part fails it is easy to access another route'.

As soon as I started to think about it, it became obvious that the term physiology covers an extremely wide range of topics but existing curriculum guidelines provided in the UK and Ireland by such bodies as the General Medical Council do not specify curriculum content. The core syllabus in physiology was developed to give a practical outline of the level of knowledge that Members of The Society believe is the minimum required by a new medical graduate who is about to embark upon a two year Foundation training.

It became clear early on that to produce a concise document I would need to reduce the scope in some way and since my own involvement in physiology teaching has been for the most part to medical students, our first efforts were directed towards them. Everyone involved recognised, however, that students of dentistry, veterinary medicine and biological sciences had overlapping but rather different needs.

A list of topics emerged from brainstorming sessions with the External Relations Committee. These were then worked on and refined by the members of the Committee and a number of others; most are Members of The Society and many are medically qualified. The first draft was available in the early summer of 2009 and a second SIG meeting was held in Dublin in July 2009. At this meeting the draft document was reviewed, some suggestions for amendments were made and a number of Members agreed to review and amend specific sections. These have now been incorporated into the document that can now be found under the Education Resources on The Society's website (www.physoc.org/corecurriculum.asp).

Since the first draft was placed on the website it has attracted many helpful suggestions and many of the proposed changes have been incorporated. Perhaps significantly, very few of those who replied to the request for suggested changes felt that too much detail was included. A large number felt that it was unbalanced and I hope that the changes made after the Dublin meeting go some way to satisfy those who made such comments.

Two important criticisms were made and I have tried to address them in the current version. The first perceived inadequacy was that the suggested curriculum 'dictated what should be taught'. This was certainly not the intention. Rather, the aim is to allow teachers to compare their own curricular goals with those of their peers. The second important comment was that if such a document were published it would come to be seen as 'all that medical students ever need to know' and that it would stifle new developments or courses that are intended to go beyond the basic 'second MB' level. Again, this was certainly not the intention. The subject continues to develop in exciting ways as all good teachers realise. Moreover, the document will need to be reviewed periodically, the suggested date for the next major review being September 2010. The authors feel strongly, however, that at whatever stage the material is taught, medical students should, at the point of entry to the F1 stage

Richard Dyball

of their training, have acquired the knowledge and understanding to explain the issues outlined. The currently available document lists all those who have made major contributions and is still regarded as 'work in progress'. I would thus welcome any suggestions for additions and further amendments (red1000@cam.ac.uk).

The further development of the curriculum has now passed from the External Relations Committee to the Education Committee under Louise Robson (l.robson@sheffield.ac.uk). Contacts have also been made with the Royal Colleges of Physicians and Surgeons and it is hoped to share expertise with these and that of the other Royal Colleges (for example the Anaesthetists). All of these bodies are concerned that physiological understanding (and understanding of other premedical disciplines) should be maintained. We hope that as the document matures it will include links to material on the websites of these and other bodies concerned in undergraduate and graduate medical education. We all need to pull in the same direction to ensure that the discipline of physiology maintains the profile it deserves and that the doctors of the future understand what they are doing and are safe.

We probably do not need audit or targets. Most people are responsible and do not want to disappoint their patients, colleagues, managers or themselves. If we set up targets some might be tempted to aim low. We seek to establish a framework of understanding upon which excellence can be built.

Richard Dyball

Department of Physiology Development and Neuroscience, University of Cambridge

In vivo pharmacology and physiology techniques: acting to increase awareness and understanding

With the sequencing of genomes and the abundance of *in vitro* data, a critical challenge in this post-genomic era is for translational work in whole animal studies that are pre-requisite to clinical applications. Unfortunately, however, there has been a progressive (and well documented) erosion of the skills base in whole animal *in vivo* experimentation over the last 20 years, resulting in a serious lack of graduates with the necessary skills to carry out this specialist research.

To help address this important problem the British Pharmacological Society (BPS) and The Physiological Society joined forces in 2001 to organise specialist training courses that enable undergraduate and some postgraduate students in the Life Sciences to gain a working understanding of experimental animal *in vivo* research principles and techniques. Three courses are run each year – one at King's College London, one at the University of Bristol and one at the University of Glasgow. Altogether the scheme costs approximately £60 000 each year to run, made possible by grants currently from the Wellcome Trust, the BBSRC and by donations from industry (notably Pfizer), with additional contingency funding from the two societies and the Integrative Pharmacology Fund.

The *in vivo* experiments in each of the three courses are tailored to suit the expertise and facilities of the host institution. However, all three courses cover fundamental principles of cardiovascular physiology, with pharmacological and neuroscience components depending on in-house expertise. The courses are run in two parts – an initial Home Office training module held during the Easter vacation, followed in the summer vacation by the hands-on practical component which runs over 5 days.

The experiments carried out are designed to include the acquisition of core skills and understanding as follows:

- An understanding of how the *in vivo* models used in the course are essential when considered in relation to complementary alternative experimental approaches.
- An appreciation of the ethical issues surrounding the use of animals in science.
- An understanding of experimental design and statistical analysis of results from the animal models used.
- Experience of use of anaesthetics and surgical techniques, including cannulation of blood vessels.
- An awareness of the integration of responses *in vivo* and of the level of concentration and expertise that such research requires.

A key factor underpinning the success of the programme has been the development of a database of academic co-ordinators who act as the first point of contact at their university to notify students of the annual call for applicants. Since the start of the scheme the courses have trained an average of 25 students each year from universities throughout the UK. Demand each year for places has grown steadily. For example, in 2009 there were 49 applications for a total of 27 places available across the three courses, representing a 14% increase on the previous year.

Students are selected on a competitive basis, including an assessment by the Steering Committee of CVs and personal statements of interest. Postgraduates and postdoctoral research scientists may also apply, but the course is intended primarily for undergraduate students who are thinking of pursuing a career in biomedical research (in academia or industry), and who would not otherwise have the opportunity to gain experience of *in vivo* experimental work at their home university.

Annual student feedback from the three courses is consistently very positive. Typically, students identify the practical elements of the course as both the most challenging aspect and the best feature. Students also greatly appreciate the contribution of postgraduate and postdoctoral demonstrators – in some cases postdocs have taken over running specific aspects of the courses, giving them a valuable opportunity to develop their own *in vivo* teaching skills. Importantly, all three courses also hold a social event, which allows the students to network informally and to get to know the staff better – especially the postgraduate demonstrators to find out more about studying for a PhD, particularly in research that involves whole animal *in vivo* approaches.

A small sample of student comments:

'*Invaluable insight into the world of* in vivo *studies and the different techniques involved*.'

'*Had much more experience in challenging practical methods which is so different to how I imagined it would be, thus I now have a realistic impression of what* in vivo *work entails*.'

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

An additional, and very consistent message from the feedback questionnaires is that the students greatly value the opportunity to obtain practical exposure to *in vivo* techniques to help determine their choice of future career. Information from students who have recently attended one of the courses supports this view – students have reported that the course inspired them to go on to postgraduate study that involves *in vivo* work.

The scheme will be running for its ninth time in 2010 and we look forward to training our next group of highly motivated and talented students. However, funding for the longer term remains uncertain, and new sponsors are needed to ensure this important training programme can continue to help fill the skills gap.

Richard Apps

A year in industry

At the start of my second year at Leeds I decided to apply for an industrial placement to help me decide whether I wanted to begin a professional career in science. Up until that point I had loved studying physiology but had no idea what I wanted to do with it once that fateful day arrived when I graduated! I applied for jobs at numerous companies and successfully landed a place in the electrophysiology department in the Neurosciences Centres of Excellence for Drug Discovery (CEDD) at GlaxoSmithKline (GSK). Once I gained the place I was very excited, but it was also an extremely daunting prospect. The move didn't only mean starting a job, in which there was a worry that I would somehow manage to destroy the lab and possibly the whole building, but it also meant making a completely new group of friends in a totally unfamiliar part of the country. The prospect became much less daunting, however, when I realised that there were plenty of students that were in exactly the same situation. A couple of months before starting the placement, we met up at a familiarisation day where I found it easy to make friends and met my housemates.

On joining the lab at GSK I entered a small, close-knit team which suited me well as they made me feel instantly welcome and I got to know them all quite quickly. They were very pleased with all of the basic lab skills that I possessed. I began experimental work within the first week, and barely left the lab from that point. This meant that my lab skills rapidly improved, along with my confidence, and within a month I was happily setting up my rig each day, patching and successfully recording currents. The great thing about learning a difficult technique like patch clamp, was that I wasn't expected to have any previous experience or be able to solve instantly any problems that occurred. As all electrophysiologists will know, there were always new problems cropping up that I had not

Laura Corns

come across before; however, there would always be my supervisor or a reliable team member on hand to help. Even though I always had support nearby, my supervisor also gave me a lot of independence, allowing me to plan my own days and decide on the direction in which I wanted to take my work. I think this was really important for me as it allowed me to develop my own style of working.

Although I had a great time during my placement there were constant reminders that I was in a corporate environment, and one that was not particularly flourishing. It felt quite difficult at times as I witnessed people become aware that their futures were uncertain while I knew I was simply leaving in a few months to return to the safety of university. At those times it was important to have the company and support of the other students; we became a close group, and despite the problems at work, we had a fantastic social life throughout the year. Being on a salary, as compared to a student loan, meant that we actually had money to spend and, since we had fixed working hours, weekends available in which to spend it. There were guaranteed nights out or some sort of social event during the weekend. Two of the most memorable times were a paintballing trip, in which my team were thoroughly and deservedly thrashed (or rather splattered), and a long weekend in Stockholm, which was one of the benefits of living 10 minutes from Stansted airport. The most fun I had throughout the year, however, was the time I spent with the rest of the girls in the netball team that we formed; we were without a doubt the shortest and worst netball team in existence but we had a brilliant time together.

As a result of these great friendships, both with the other students and my team, I was very sad when I realised that the year was nearly over and I'd soon have to leave GSK and return to university. It was almost as strange moving back to university as it was starting my industrial year in the first place. However, when it came to starting my final year studies, I was pleasantly surprised at how the year in industry had affected me, as were the other students who'd also taken this year out. We had clearly developed a different attitude towards our studies compared with the majority of students that had progressed straight from second to third year. We had more confidence in our practical and presentation skills and, most strikingly, had a better work ethic. To students that had progressed straight to third year, managing a 9-to-5 day appeared excruciatingly painful, but to us it had become the norm.

I would like to think that I would have had a successful third year had I not taken a year in industry, but in truth I don't think that I would have reached quite the same level of academic achievement if it wasn't for that experience. If I were given the choice again I would definitely do the year in industry and I would heartily recommend it to other students facing the same choice. It gave me great practical training, experience of full time work, the chance to make useful contacts and, best of all, made me realise that working in science is exactly where I want to be.

Laura Corns

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 The Physiological Society Publications Office (magazine@physoc.org) with your suggestions.

Cardiff University Physiological Society

Whilst contemplating the fruit content of a Christmas pudding and convincing themselves that it really could count as one of their 'five-a-day', a group of final year physiology students at a Christmas party in 2008 decided to set up the Cardiff University Physiological Society. Now in its second year as a society, outgoing President Stuart Hanmer, and incoming President James Selvey discuss the activities of the society, and give their hopes for the future.

Our main motivation for forming the Cardiff University Physiological Society (CUPS) was to bring together all physiologists and other students studying physiology (including biomedical scientists, anatomists and intercalating medical students) in Cardiff University's School of Biosciences. Students find the modular nature of the biosciences schemes at the university good from an academic point of view, especially in terms of giving a wide knowledge base in the first year, but socially they can be a nightmare! The smallest lectures still have hundreds of students from a wide range of degree schemes, so it can be difficult to meet people: it's a 'water, water, everywhere' scenario.

One of the primary aims of CUPS is to work on the social side and get physiologists meeting each other in the first year, so as not to be surprised to find that other people study physiology too. Variety is the spice of life, and through a combination of careers sessions and the obligatory fancy dress-based socials, we think we are achieving this. One of the highlights of the society's first year was our Biomedical Sciences Careers Evening. We aimed to have a selection of speakers representing a range of different disciplines, both clinical and academic. To this end, we invited a dietician, a PhD student and a trainee clinical haematologist. This event was a great success, with around 60 students attending, all eager to ask as many questions as possible as the thought of exams loomed. As with any large event, the requirement for pizza is (theoretically) directly proportional to the number of students. Sadly, this formula seems to be flawed when faced with physiology students. We have learnt our lesson for the next careers evening scheduled early in 2010, which we hope will attract even more students eager to find out where their physiology degree can take them.

The Cardiff University Physiological Society logo, complete with (artistically licenced) action potential.

On the social side, the once-annual physiology Christmas meal for students and staff has been re-kindled by CUPS and has so far been a great success. Our most recent meal also welcomed Ole Petersen FRS, who takes on his new role as Director of the School of Biosciences early in 2010. We are now hoping to establish a summer ball in the Cardiff School of Biosciences. This should be a fantastic opportunity for students to get to know each other outside of the lecture theatre.

The Physiological Society proper was helpful in establishing our student society. Early in 2009, Irrum Magre, who was then The Physiological Society's Membership and Education Co-ordinator, very kindly came to speak to us and give us an idea of what the Physoc could offer us in terms of support. As we continue to find our feet, we aim to form closer associations with The Physiological Society, providing undergraduates with the opportunity to visit conferences and get involved with physiology outside of Cardiff University (see p. 48).

As with any new idea, there are bound to be difficulties in the beginning. We have been fortunate in that these have been relatively few and far between. The initial problem of gathering together physiologists is easily solved through speaking to staff who have regular contact with students. Sending out emails to year groups and creating a Facebook page also helped raise our society's head above the parapets. However, once we had an interested group of students, the delicate issue of money came about. To help raise funds we have asked for an annual fee of £2. So far this money has helped pay for advertising material and the all-important food we have previously mentioned. We feel that this fee is fantastic value, and also helps us get discounted rates for society merchandise such as hoodies, which we hope to be sporting before the summer.

Momentum is important in setting up any kind of society. After the initial excitement of getting members and hosting a successful event, the onus is on ensuring that this enthusiasm is maintained throughout the year, and continues on into future years. Thankfully, this has not been a problem for CUPS. The ability to shape their own society, especially one founded so recently, has proved an enticing prospect for physiology students. After all, being involved in something new is always more exciting than rehashing the old – that's why, as they so diplomatically say, they picked physiology over history.

So what does the future hold for CUPS? We hope that as the society becomes more well known in the School of Biosciences that we can expand our numbers and help students, should they so wish, get an idea of what physiology might offer as a career. However, we do not want to restrict ourselves to undergraduates. Postgraduate students will also benefit from what we have to offer as a society, and we hope that we can provide help to them, also. Charity work is also an area which we would like to get involved in, as is promoting the study of physiology in local schools. As Niels Bohr once said, 'Prediction is very difficult, especially about the future'. This is certainly true, but we have a very good idea about what we would like to be doing.

Stuart Hanmer and James Selvey

The resounding success of a new undergraduate initiative

On 14th November 2009, Keble College, Oxford hosted the first Undergraduate Physiological Sciences Conference (UPSC) – a one-day event organised by and designed especially for undergraduate physiologists.

The first UPSC welcomed over 130 undergraduates from 34 different universities across the UK and Ireland. Welcoming talks by Ania Szmuksta, lead organiser, and Michael Collis, Chief Executive of The Physiological Society, were followed by rousing and enlightening keynote lectures by Denis Noble CBE FRS and Julian Paton. The students also attended careers sessions for which Mary Morrell, in collaboration with the Oxford Careers Service, presented an excellent CV workshop and Clare McVicker of the Wellcome Trust, Daniel Rosen and Daniel Kumpik, graduate Oxford scientists, drew attention to the many options that await those considering doctoral research. The conference also attracted several senior scientists from the Oxford academic scene and beyond, who joined the undergraduates for the poster session and for the careers and networking evening.

One of the highlights of the day was the student poster session for which over 50 entries were received. The panel of judges commented on the high standard of the posters, and considered most to be comparable to those presented at professional specialist meetings. The first poster prize was awarded to Nishanthan Manickavasagar from King's College London for 'Subcellular localisation of the NADPH oxidase isoform Nox4 in cells of the cardiovascular system.' The abstracts submitted by the undergraduates were also used to select one student to present a short prize talk. This was awarded to Anna Graca from the University of Aberdeen, who spoke on 'PLD-coupled mGluRs modulation of synaptic-like vesicle recycling and afferent discharge frequency in mouse mechanosensory terminals.' The evening was rounded off by a dinner at Freud's restaurant, with many delegates choosing to stay on and explore the Oxford nightlife.

An Oxford physiologist, David Thomson, talking to Denis Noble at the Natural History Museum.

The organising committee (from the left): Lauren Parker, Chloe Lim, Ania Szmuksta, Claire Machin and Charlotte Whicher.

Student feedback revealed a very positive reception of the meeting with nearly 90% of the respondents expressing interest in attending future UPSCs. The attendees not only complimented the contribution of invited speakers, but also the performance of the undergraduate organisers; indeed Professor Noble considered the meeting went as smoothly as similar events run by 'professionals'.

The organising committee would like to thank The Physiological Society, the British Society for Neuroendocrinology, the University of Oxford and Peprotech for their generous financial support, with special thanks to Chrissy Stokes at The Physiological Society for her invaluable help.

The post-conference materials including the photo gallery, the abstract book and the slides from the presented sessions, are now available to download from the UPSC website:

www.ouphysoc.co.uk/upsc2009

Ania Szmuksta
(Lead organiser)

Undergraduate membership

The Society supports Undergraduate Members by offering the following benefits:

- Free attendance at Society meetings
- Travel grants
- Funding to host a seminar
- Techniques Workshops
- Opportunity to apply to host an Undergraduate Conference
- Networking opportunities
- Hard-copy of *Physiology News*

Applicants must be studying for a degree in physiology (or a related subject).

For more information, please email membership@physoc.org

Exercise physiology sixth form workshop

The Department of Biomolecular and Sport Sciences at Coventry University hosted a workshop aimed at students studying exercise physiology as part of their 'A' level or BTEC National Diploma studies. The workshop was designed to excite and inspire these students so that they may consider a career in exercise physiology or a related area. Content included the effects of exercise on the respiratory system, the physiology of jumping, and the Douglas bag technique to determine oxygen uptake and energy expenditure. Laboratory activities were designed to be very 'hands-on' and allowed the students to use equipment they would not normally have access to in their school/college.

The workshop began with an introductory talk on further study and career opportunities involving exercise physiology. Students were then divided into three groups to rotate around three laboratory sessions.

The oxygen uptake and energy expenditure lab session was taught by Mike Price. Students used Douglas bags to collect expired air at rest (5 minute collections) in order to calculate resting oxygen uptake and energy expenditure. Each student had the opportunity to analyse their own Douglas bags using gas analysis equipment – something that schools do not usually have available.

On your bike! Investigating the effect of exercise on respiratory volumes.

Measurement of resting respiratory volumes using the spirometer.

Determination of jump height using teh jump mat.

The physiology of jumping performance was taught by Rob James. In this session, the students measured their vertical jump height using a jump mat to investigate factors that could determine jump performance, length and strength of their leg, and also their hand-grip strength. Data from the entire class showed that those who had the longest legs, the strongest legs and were generally strong overall (as indicated by hand-grip strength), had the highest jump performance.

The lab session investigating respiratory volumes was taught by Sadie Dean. The aim of this session was to investigate the different respiratory volumes that can be measured in lung function testing using spirometers and peak flow meters. It also looked at how respiratory volumes change (but not the overall capacity) with exercise, requiring the students to exercise on the cycle ergometers.

Feedback from the students and teachers was very positive; this was very pleasing to hear after all the hard work that went into organising and delivering the day. A big thank you to everyone involved, to Angela Breslin from The Physiological Society, and to The Physiological Society for sponsoring the event.

Jayne Hastings
Associate Head (Development)
Department of Biomolecular and Sport Sciences, Coventry University

The outreach grant scheme is open to all Members and Affiliates of The Society who would like to communicate the excitement of physiology to young scientists and the wider community. For more information, please visit our website or email education@physoc.org

Get involved and write an article for *Physiology News*

Have you done something in your studies you would like to recommend to other young scientists, attended an amazing training course or got an issue you'd like to get off your chest? If you enjoy writing then why not contribute to *Physiology News*. We have an annual prize of £200 for the best published article written by an Affiliate or young scientist. If that isn't enough incentive, contributing to the magazine is a great extra on your CV and a nice way to tell a broader audience about the things you do. We are always looking for people to contribute to the Affiliate pages in the magazine and would love to hear from anyone who would like to get involved.

Email us for more information or to discuss ideas at:

magazine@physoc.org

Young Physiologists' Symposium

23–24 September, Leicester. Ion channels and receptors in cell physiology

Symposium photo on the lawns of Stamford Hall. Sitting on the bench from left to right: Noel Davies, Martyn Mahaut-Smith, Steve Watson, John Challiss, Ian Forsythe, David Brown and standing on the right John Mitcheson.

The late summer's sun pouring across the perfectly manicured lawns of Stamford Hall at the University of Leicester and the tranquil nature of the registration desk masked the shear panic that lay in my chest. After a year of planning, and with over 120 people registered, I was wondering if anyone would turn up? As Kevin Costner found out in *Field of Dreams* – if you build it, they will come. Sure enough, by the time the welcome address was due to start we had a full house.

Leicester's own John Challiss kicked things off with an insightful talk on glutamate receptors. There then followed four good talks by young physiologists to complete the Receptors in Neuroscience session. The second session, Cardiovascular Ion Channels was opened by Godfrey Smith (University of Glasgow). As ever, he presented high-level science in a manner that held everyone's interest. The rest of the session was taken up by four talks from PhD students and post-docs.

The poster session and drinks reception was a lively affair, which got livelier as more wine and Pimm's were consumed. Lots of people were debating the merits or otherwise of different techniques and approaches. The symposium dinner followed the poster session. Over the four courses of dinner there were more conversations and some joke telling. After dinner everyone retired to the bar where the hardest test of the day was to take place: the pub quiz. Over five rounds, the teams were locked in a battle of trivia. Although there was only one winning team, a good time was had by all. Alongside the quiz there was a magician on hand to dazzle and wow the crowds with close-up tricks.

Day two began with Steve Watson (Birmingham University) giving his plenary talk in the Cardiovascular Receptors session, which was followed by four talks by young physiologists. After a coffee break, the Ion Channels in Neuroscience session started with David Brown (UCL) who delivered a great talk, full of first-rate science and funny to boot. Four more talks by early-career scientists followed and brought to an end the Leicester Young Physiologists' Symposium.

The prize for the best talk was given to Matt Barker (University of Leicester) for his talk 'Vestibular projections to the dorsal cochlear nucleus are characterised by the vesticular glutamate transporter VGLUT-2'. There were two winners for the poster prize: Chunjing Gu (University of Cambridge) and Rubia Araujo (University of Nottingham).

I would like to thank the staff in the Department of Cell Physiology and Pharmacology, particularly Jacqui Noon, Alan Willcocks, Blair Grubb and John Mitcheson. Thanks also go to the guest speakers and, of course, the rest of the organising committee.

Steve Thomson
University of Leicester

Industrial experience – a stepping-stone on the pathway to career success?

Research in physiology can be tough and is highly competitive. To be an effective and successful researcher requires a huge range of skills, including both the intellect and practical aptitude to undertake the research itself and also related skills required for communicating and publishing your work, collaborating with other researchers and managing your projects to a successful conclusion. Whilst many of these skills can and often are learned during the training undertaken for a PhD and in postdoctoral work, there is much to be said for gaining experience and skills from a range of different research environments in order to achieve more balance in your skillset.

As I prepared to write this article, I was also planning my next career move as part of a relocation plan to London or the South East. When assessing my future options, I also considered my own experiences during my degree, PhD and postdoctoral career and the advantages I have gained from these experiences. As a researcher who has spent time working in a range of academic and industrial labs at large and small institutions and companies, what struck me most was how the time I had spent in industry had helped to shape my research attitudes and ideas, and helped me to develop skills that are benefitting me today, despite making a move back into an academic research position.

Research in the pharmaceutical industry is very disease-focused and as such, experts with specific knowledge in the underlying physiology and related laboratory techniques are often sought for research programmes in specific disease areas including cardiovascular, musculoskeletal, neurological, respiratory and gastrointestinal disorders which represent major research efforts for many of the big pharma companies. For many physiology researchers, having this immediate disease relevance provides an important driving force for their work. From a personal perspective, the goal-led approach to research projects that I have encountered in industry has allowed me to develop a more focused approach to my own research work. Industry has shown me the other end of the research spectrum, allowing me to view my research from a wider angle as a small part in a much larger picture.

Industry projects are often multi-disciplinary and this team-based approach means that projects move more quickly and with much more interaction with others than is often seen in academic labs. The collaborative team-based environment helps to develop people management and good communication skills, essential for those wanting to progress to become group leaders. There are also opportunities to gain specific scientific expertise through industrial experience, including access to cutting-edge equipment, exposure to new techniques and the chance to undertake additional training courses to develop specific additional skills.

So, how to gain experience in an industrial research setting? For under-graduate and PhD students, there are a number of opportunities such as sandwich or summer placements and the CASE PhD studentships that are partially funded by an industry partner and allow students to spend time working in the partner company during their PhD.

At the postdoctoral level there are a number of fellowship opportunities, such as the Royal Society Industry Fellowship (www.royalsociety.org), that are specifically designed to allow an academic scientist to work on a collaborative project with an industrial partner, gaining valuable industrial experience and making industry connections that can live on even after the fellow returns to their home institution.

A number of the big pharma or biotech companies are now offering fellowship schemes aimed at recruiting postdoctoral researchers; for example, Novartis, Genentech and Millenium Pharmaceuticals all offer postdoctoral fellowship programmes. Such schemes often involve dual mentorship from academic and industry advisors, and are intended to contain a significant portion of preclinical basic research. Postdocs on such schemes experience life in industry and have access to the funds and equipment that industry offers whilst still pursuing an academic-linked project. Fellows are expected to publish in peer-reviewed journals and present data at scientific meetings in exactly the same way as they would expect to if working in an academic lab.

Sam Passey

At the end of such a scheme, usually 3 years, postdocs have the choice of returning to academia taking with them the valuable industrial experience they have gained, or seeking employment in an industrial setting with the benefit of already having 3 years of solid industrial experience under their belts.

If you don't want to leave your current position but are curious about life in industry, there may still be opportunities to link to industry and perhaps gain some experience there. Does your research offer any commercial benefit that you could develop further with a suitable industrial partner? Does your supervisor or any colleagues have existing industry contacts in a relevant field that might be used to set up a short-term placement in the company or some collaborative research? Many universities now have 'knowledge transfer' departments that specialise in managing and developing links between academia and industry, so these may provide a useful starting point for those interested in making new links with industry.

Of course, there are downsides that one must consider about research in industry; for example, opportunities to publish primary research papers may be restricted depending on the research field and the company involved, and issues regarding confidentiality and intellectual property that some people may find difficult. In addition, there may be less freedom to pursue interesting lines of investigation if they do not fit directly within the remit of the research programme. However, for those looking to apply their physiology skills and contribute to a larger research programme with more immediate physiological relevance to actual patients, even a short spell of research in a pharmaceutical or biotech company may enhance their skillset and who knows – it may even pave the way to new and exciting career opportunities.

Sam Passey

Experimental Physiology
Translation and Integration
A publication of The Physiological Society

New Editors for *Experimental Physiology* in 2010

Marc Kaufman

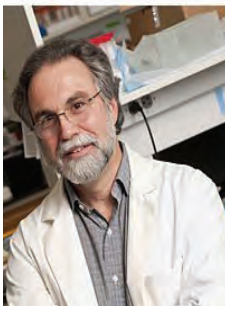
Marc received his PhD in Physiological Psychology in 1977 from the University Miami. He spent the next three years as a postdoctoral fellow in the Cardiovascular Research Institute at the University of California San Francisco working in the laboratory of Hazel and John Coleridge. His first faculty position was at the University of Texas Southwestern Medical Center where he investigated neural control of the circulation during exercise under the mentorship of Jere H Mitchell. Currently, Marc is the Research Associate Director of the Penn State Heart and Vascular Institute in Hershey, PA, USA. His research focuses on the exercise pressor reflex which arises from contracting skeletal muscle and which functions to increase sympathetic discharge to multiple vascular beds. Particular attention is paid to the mechanical and metabolic stimuli arising in both health and disease that activate the thin fibre muscle afferents comprising the sensory arm of the reflex.

Andrew McCulloch

Andrew McCulloch is Professor of Bioengineering and Jacobs School Distinguished Scholar at the University of California San Diego, where he joined the faculty in 1987. He is a member of the UCSD Institute for Engineering in Medicine, the California Institute for Telecommunications and Information Technology, a Senior Fellow of the San Diego Supercomputer Center, and a member of the UCSD Center for Research on Biological Systems. Dr McCulloch is a Principal Investigator of the National Biomedical Computation Resource and Co-Director of the Cardiac Biomedical Science and Engineering Center at UCSD. He served as Vice Chair of the Bioengineering Department from 2002 to 2005 and Chair from 2005 to 2008. Dr McCulloch is Director of the HHMI-NIBIB Interfaces Graduate Training Program and the accompanying UCSD Interdisciplinary PhD Specialization in Multi-scale Biology.

Dr McCulloch was educated at the University of Auckland, New Zealand in Engineering Science and Physiology receiving his PhD in 1986. He was an NSF Presidential Young Investigator and is a Fellow of the American Institute for Medical and Biological Engineering. He has served on the Board of Directors of the Bio-Medical Engineering Society, and is currently Associate Editor of the *Medical and Biological Engineering and Computing* and *PLoS Computational Biology* and co-Editor-in-Chief of *Drug Discovery Today: Disease Models*. He is on the editorial boards of the *American Journal of Physiology: Heart and Circulatory Physiology* and *Computer Methods in Biomechanics and Biomedical Engineering* and *Cellular and Molecular Bioengineering*. Recently, he has given the Konrad Witzig Memorial Lecture and the Donald Wassenberg Memorial Lecture.

Dr McCulloch's lab uses experimental and computational models to investigate the relationships between the cellular and extracellular structure of cardiac muscle and the electrical and mechanical function of the whole heart during ventricular remodelling, and arrhythmia. Dr McCulloch is a PI on the NCRR-supported National Biomedical Computation Resource, and has grants from the NHLBI, NSF and UC Discovery on cardiac tissue engineering, ventricular biomechanics, signalling pathways in cardiac hypertrophy and failure, cardiac electromechanical interactions, and computational cardiac biology.



Gregg Semenza

Dr Semenza received undergraduate training in Biology at Harvard College; MD and PhD degrees from the University of Pennsylvania; pediatrics residency training at Duke University; and postdoctoral training in Medical Genetics at the Johns Hopkins University School of Medicine, where he has spent his entire career. He is currently the C. Michael Armstrong Professor at Johns Hopkins with appointments in Pediatrics, Medicine, Oncology, Radiation Oncology, Biological Chemistry, and the Institute of Medical Genetics. Since 2003 he has served as founding Director of the Vascular Program in the Johns Hopkins Institute for Cell Engineering. Dr Semenza's laboratory identified hypoxia-inducible factor 1 (HIF-1), a protein that allows cells to respond to changes in oxygen availability. The purification of HIF-1 in 1995 opened the field of oxygen biology to molecular analysis and has revealed major roles for HIF-1 in many developmental, physiological and pathological processes. In collaboration with the laboratory of Nanduri Prabhakar,

the critical role of HIF-1 in oxygen sensing by the carotid body has been demonstrated and linked to the pathogenesis of systemic hypertension in response to chronic intermittent hypoxia. Dr Semenza serves on the editorial boards of *Antioxidants and Redox Signaling*, *Cancer Research*, *Cardiovascular Research*, *Circulation Research*, *Journal of Clinical Investigation*, *Molecular and Cellular Biology*, *Molecular Cancer Therapeutics*, and *Oncogene*. He is Editor-in-Chief of the *Journal of Molecular Medicine*. He has been elected to the Society for Pediatric Research, American Society for Clinical Investigation, Association of American Physicians, and the National Academy of Sciences, USA.

Xi-Yong Yu

Professor Yu engages in the research field of molecular cardiology and pathophysiology. His main research interests include chronic heart failure and diabetic cardiomyopathy comprising three research aspects: (1) gene therapy and stem cell therapy in heart repair; (2) the role of pro-inflammatory cytokines in the development of cardiovascular disease; (3) epigenetics and pharmacogenomics in cardiology.

He has published more than 300 papers in academic journals at home and abroad, published 7 books, and received 6 National invention patents. He has undertaken more than 20 research projects from the National Natural Science Foundation, the Provincial Natural Science Fund and other scientific and technological programs. Professor Yu won 5 Medical and Health Progress Awards, and 3 Science and Technology Awards from Guangdong Provincial Government. He has also been awarded one of the academic and technology leaders of medical science and education project in Guangdong Province, the national outstanding young experts in Chinese and Western integrative medicine, the title of Glaxo Award for outstanding young doctors, the Ten Outstanding Young Persons in Guangdong Province Nomination Award, the State Department experts in special government allowances, and the Guangdong provincial authorities forefront positions.

Experimental Physiology Winter Games Themed Issue

The March issue of *Experimental Physiology* (published in February) contains a series of articles that provide an insight into elite human performance in the unique, and often spectacular, environments associated with the Winter Olympics.

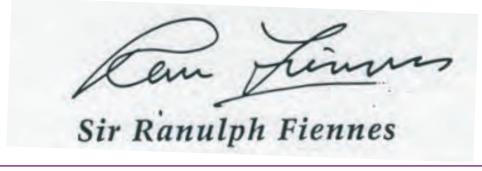
When most people think about these Games we conjure up glorious images of snow and high mountains; but when physiologists think of cold and altitude, most immediately think of environmental challenges including hypothermia and hypoxia. We have encouraged review authors to resist stereotypical thought progression and avoid the standard, and perhaps dated, tactic of examining each of the major physiological systems in

turn with the aim of identifying limiting factors to performance. Our intention, therefore, was to invite submissions from those with a novel, insightful and most importantly, integrative, view of the limitations to performance in Winter Olympic sport. We are delighted with the unique collection of articles, clearly demonstrating that the physiology of a medal-winning performance in many winter sports is still far from fully understood.

If one examines skiing and skating, a fall is always possible, but the important question is whether

Sir Ranulph Fiennes expresses his support for the *Experimental Physiology* 2010 Winter Games Themed issue

I am very pleased to see this collection of articles that contain so much excellent information about an area that has long interested me, that of how we humans can perform so well under extreme conditions, resulting from either physical exertions and/or environmental stress. This timely issue of Experimental Physiology explores the current understanding of how our bodies react when internal and external challenges are combined, and provides a fascinating insight into how finely tuned our responses must be to achieve our set goals whether as athletes or explorers. Whilst it is surprising to me how much we do already know, these papers also identify where our knowledge is inadequate to allow a full mechanistic explanation and indeed how much more research needs to be done. However, it is particularly gratifying to see how information from different disciplines is being harnessed to this end.



or not the fall was preventable. If it resulted from muscle fatigue or failure to execute a motor programme correctly, the probable answer to this question is yes, and these are preventable circumstances. Richard Fergusson points out that a well-rehearsed motor programme assumes a certain force output at a specific time from activated motor units. If this is not the case then, in the split second available to correct an error or react to an unexpected change in terrain, all is lost. He explains how force output could be depressed, or recruitment strategy could be altered, during exercise under ischaemic conditions. Since contractile forces as low as 20% of maximal will occlude blood supply to human calf muscles and quadriceps, it is easy to imagine exercise conditions where this occurs (e.g. the low tuck position of a downhill skier). In other circumstances, force may be dramatically reduced at low frequencies of stimulation, which can last for up to 48 hours post-exercise. The influence of such low-frequency fatigue from an unexpectedly difficult qualifying event (such as ice hockey) on the medal deciding rounds is evident. Ben Levine explains how motor programmes in many events need to be retrained to take account of the lower resistance encountered when moving through air at altitude. His example of the shorter time taken to rotate the body during a spin in ice dance is compelling. Proper allowance for a period of acclimatisation to these environmental conditions must be included in the preparation schedules for competition and also, importantly, on return to normal training back at lower altitudes. Failure to allow this time is likely to increase the risk of potentially serious injury in a fall or incorrect landing.

While recruitment of motor units is modulated by muscle ischaemia, this may be mediated by afferent feedback to the motor pool or brain. The role of muscle afferent feedback in driving sympathetic vasoconstrictor tone to active and inactive muscles (Bill Sheel), as well as the role of mechanoreceptive afferent feedback in baroreflex function and cardiac vagal tone (John Coote), reveal the extent to which truly integrative physiology is required to allow fine control to compensate for conflicting stimuli. The biathlon is an obvious example of where high aerobic capacity is a prerequisite for success, and the role and limitations to performance set by the respiratory system at altitude and in the cold (Bill Sheel), and how the cardiorespiratory system adapts to training (John Coote) and altitude (Ben Levine), are explored. However, the biathlon also involves accurate shooting. Missing a target incurs a time and effort penalty added by skiing a lap of a circuit, and this invariably influences the outcome of a race. At this point Martin Lakie's expertise on tremor and John Coote's understanding of heart rate recovery post-exercise come to the fore. It is clear from these articles that we still don't know whether a high or low pulse rate during shooting, especially in the standing position, is advantageous in terms of performance. The mechanical correlates of the heart beat and pulse wave propagation through the arm have obvious consequences for accurate sighting on the target. Whether this error can be avoided, by having rapid heart rate recovery and so potentially a longer interpulse interval during which to shoot, or simply minimised, by having a higher heart rate (lower stoke volume and hence smaller cardio-ballistic effects) is debated.

Intense exercise at altitude may place an extra strain on energy supply at a time of reduced mechanical efficiency due to low temperature. Martin Flueck provides a timely appeal to consider the feed-forward as well as feed-back origin of metabolic malleability in response to endurance training at altitude, highlighting the genomic and environmental interactions that underlie inter-individual differences in performance. Daniel Martin and colleagues utilise ascent of Everest to explore the range of adaptive physiological responses that ameliorate a fall in tissue oxygen delivery at altitude. How these processes are modified during acclimatisation, and their effect on work capacity is examined, changes that cannot be explained solely on the basis of blood P_{O_2} alone. Thus, new avenues of discovery from recreational exertion may provide insight into the genetic and physiological makeup of elite winter athletes that ultimately determine individual performance.

The full issue is now online at:
http://ep.physoc.org/content/95/3.toc

Experimental Physiology would like to congratulate Peter Hunter FRS (Consulting Editor) on wining The Rutherfold Medal which is New Zealand's highest science honour, along with being made MBNZ in the Queen's New Year Honours in New Zealand for Services to Science.

The Journal of Physiology

New features in 2010

The Journal of Physiology has introduced three new features this year which aim to provide useful additional information for both specialist and non-specialist readers.

The online Table of Contents (eTOC) of each issue now carries a non-technical summary of all research papers in the issue. The idea behind this feature is that individuals such as students, patients, carers or journalists who are searching the internet for information about physiological terms may come across the abstracts of *Journal* papers but be unable to understand what the paper is about. The non-technical summary will give them this

information in easily comprehensible language and should help to spread a better understanding of physiology amongst the general public.

Review articles in *The Journal* now include author profiles. A photograph and a short biography of the main author of the review at the start of the review helps readers to put the article into the context of the author's expertise and interests. It may also boost interest in the articles from readers who follow the publications of leaders in their field.

Finally we have introduced an experimental series of interviews with eminent physiologists. Editor Brian Robertson interviewed and photographed Eric Kandel for our first article. The highly formalised style of scientific reporting precludes any familiarity with the people behind the experiments. Our interview answers many of the questions that readers of Kandel's numerous scientific papers may have considered as they wonder what it takes to become a leading scientific researcher.The charming portraits taken by Brian offer additional insights into the person behind the science.

New Council Member

In the previous issue of *Physiology News* (PN77, pp. 51–53), many of the new Council Members for 2009 were included. Here we have answers to the same questions from Julian Dow.

Julian Dow

What is your current job(s) title?

Professor of Molecular and Integrative Physiology, and Chair of Integrative and Systems Biology research theme, University of Glasgow; and visiting Research Professor in Medical and Molecular Genetic Research, King Saud University, Riyadh

Summarise your career to date

I took a BA in Natural Sciences, University of Cambridge (1977), and stayed on for a PhD in Zoology (1981), working on ion transport in insects with Simon Maddrell. I was then awarded a Harkness Fellowship, which I took at Temple University, Philadelphia, working on what would later be known as the V-ATPase. On my return, I took up a Research Fellowship of St Catharine's College Cambridge, for a year, before being appointed a Lecturer in Cell Biology, at the University of Glasgow in 1984. After moving around a little, I became a professor in 1999, and served a term as Head of the Division of Molecular Genetics. I was awarded ScD by the University of Cambridge in 2007. I presently head the research theme of Integrative and Systems Biology.

What is the best thing about your current position?

Variety.

What is the worst thing about your current position?

Nothing.

What is the biggest issue facing young physiologists today?

The extraordinary toughness of the career path, in the context of the present financial climate.

Why did you stand for Council?

I care very much about the future of physiology.

Which areas of Council or Society activity would you most like to get involved in?

I am particularly excited about the intersection between physiology and genetics. For most of us, the functional and molecular paths are mutually exclusive from early in our undergraduate careers, and I think this limits our opportunities.

What is your favourite(s) saying or quotation (and who said it)?

'Always look on the bright side of life.' (Eric Idle in '*Monty Python's Life of Brian*')

What is the most important thing life has taught you?

Try to seize opportunities – life is so short that there's rarely a second chance.

Which other scientist (living or dead) would you like to have been, and why?

August Krogh: he effectively founded modern comparative physiology, and got a Nobel laureate to boot. If I hadn't chosen him, it might have been his son-in-law (Knut Schmidt-Nielsen).

New staff member

Maev Fitzpatrick

I have moved a long way from my home in Cronulla, Sydney, to join *The Journal of Physiology*'s publications office in Cambridge.

While surfing my way around Australia and hiking through New Zealand, I studied for my BA degree in English and my BSc degree in Anatomy at the University of New South Wales. During this time I gained an interest in science and publishing.

After a period working in the health department and hospitals in Sydney, I decided to pack my bag and take a chance in the UK. I arrived in August to catch the end of an English 'summer' and soon found myself surfing around Bordeaux and Biarritz, walking in Provence and visiting the pubs of Ireland...before starting this great opportunity with *The Journal*. I am really enjoying working and living in Cambridge despite the serious lack of surf. It was very exciting building my first snowman before Christmas!

John Spence Gillespie

1926–2009

John Spence Gillespie, who died on November 8th 2009, at the age of 83, was Professor of Pharmacology at Glasgow University from 1968 to 1992. He was the founding Head of the Department of Pharmacology from its inception in 1968 until 1988, and served as Vice-Principal of the University from 1983 to 1991 and Dean of Faculties from 1995 until 1998. He served as Chairman of MRC Grants Committees, on the Committees of both the British Pharmacological Society (BPS) and The Physiological Society and, as BPS representative, on the Editorial Board of *Pharmacological Reviews* and on the Editorial Board for Monographs of The Physiological Society. He was Honorary Secretary of The Physiological Society from 1966 to 1972 and was a Fellow of the Royal Society of Edinburgh.

John spent his childhood in the industrial towns on the Clyde downstream from Glasgow, where his education was disrupted by illness and the effects of the blitz. Nevertheless, he qualified in Medicine at Glasgow University in 1949 and, after National Service, entered a research career. This was initially intended as a temporary measure to aid his ability to practice medicine, but he never escaped its allure. He gained his PhD working on the innervation of the colon under RC Garry at the Institute of Physiology in Glasgow then spent a productive period with GL Brown at University College London (UCL). Together these mentors kindled his interest in the known and, at that time, unknown, neurotransmitters in the peripheral autonomic nervous system. Like many of us, he constantly returned to the writings of Langley and his contemporaries when discussing these matters, as revealed in a recent interview in the Archives of The Physiological Society.

His partial shift of focus from physiology to pharmacology is shown by his output of research papers: roughly one per year in *The Journal of Physiology* between 1954 and 1983 and a similar production in *British Journal of Pharmacology* 1962–94. Indeed, his research switched direction several times. After UCL, in 1959 he went to the Rockefeller Institute in New York to add electrophysiology to his armamentarium. He was to return to this in the 70s when Kate Creed spent a producutive spell in Glasgow. However, on his return to Glasgow, he soon returned to his fascination with the fate of neurotransmitters after

release, stimulated by his work with Brown. That led to an interest in the extraneuronal uptake of transmitters, which he pursued with the then new fluorescence microscopy technique of Falck & Hillarp that made noradrenaline fluorescent so that it could be seen and measured in all cell types. He pursued this method with some zest, obtaining a large grant to purchase a microspectrograph, a huge machine that could carry-out quantitative spectrographic analysis that could distinguish various fluorophores derived from chemically related substances, i.e. noradrenaline, adrenaline, dopamine, 5-hydroxytryptamine and so on. This was long before the development of modern techniques to visualize these differences down the microscope. However, his team suffered the usual early-adopter problem that the machine was forever breaking down and, as far as I am aware, no published result ever emerged. Nevertheless, while doing simple histochemistry with the same technique, *circa* 1970, he came across the rat anococcygeus muscle, largely because it was full of fluorescent noradrenergic nerves. This fascinated him, of course, because the previous person to mention the muscle was Langley.

This little preparation offered-up a powerful non-adrenergic, non-cholinergic (NANC) nerve response, which took him back to some of the puzzles in his PhD project on the colon and, of course, Langley. The rest of his research career consisted of pursuing the nature and properties of the underlying transmitter. After a largely futile decade of hitting various assistants' heads (including mine) off the brick wall of 'what was this transmitter?', progress was made with the successful production of a smooth muscle relaxant extract of anococcygeus or the conveniently associated but much larger bovine retractor penis, in collaboration mainly with Billy Martin and Ann Bowman. They went on to demonstrate that both the extract and NANC transmission were susceptible to haemoglobin. Of course, with the advent of EDRF and nitric oxide, the phenomenon was shown to be nitrergic transmission and the explanation for the long and painful failure to bioassay a transmitter that was a gas, became clear.

Alongside this scientific career, John ran the gamut of the pressures that attend academic life, particularly if intelligent and thoughtful, as he was. He took on the job of creating a new Pharmacology Department in Glasgow just after taking up the post of Secretary of The Physiological Society. Both jobs went well. The Physoc is still a going concern despite the efforts of some of his successors and he created a remarkably cohesive and successful Pharmacology Department with a loyal and devoted staff. His twenty year tenure is regarded as a golden period by his staff and by those who took their BSc or PhD degrees during that time. Many have followed distinguished careers in universities and pharmaceutical companies throughout the world.

Towards the end of his career, John was sucked into senior university administration as Vice Principal (Pro-Vice Chancellor, for Sassenachs) for two terms, surely unnatural punishment. He said in his recent interview that he never enjoyed this but he was extremely well respected and considered fair and even-handed, accounting for his second term in the position. Actually, this characteristic could be infuriating if you ever got into an argument with him. Even more than other academics, he could see six sides of an argument and once you wore them down, a seventh.

Unlike many, John Gillespie did not haunt his department after retiring. He took up his interests in painting and gardening, and delighting in his grandchildren. He advised subsequent Principals while holding the ceremonial post of Dean of Faculties. And he left the rest of us to get on with it. This is another lesson that many could learn from him.

He is survived by his wife, Mina, whom he married in 1956, sons David, Graeme, Adrian and Ian, daughter Ruth and seven grandchildren.

Ian McGrath

An obituary by Tom Muir and Billy Martin was published in the Glasgow Herald on 12th November 2009:

http://tinyurl.com/ybsqcsn

Main Meeting of The Physiological Society

Physiology 2010

30 June - 2 July 2010

University of Manchester, UK

Scientific symposia

Poster and oral communications

Trade exhibition

Plenary lectures, including:

Murray Esler
Baker Heart Research Institute, Melbourne, Australia

Nancy Rothwell
University of Manchester, UK

Roger Nicoll
University of California, San Francisco, USA

Roger Y Tsien
University of California, San Diego, USA

Kay Davies
University of Oxford, UK

Abstract submission opens 1 March 2010

Abstract submission closes 31 March 2010

Registration now open

www.physiology2010.org

New techniques workshops

The Society is launching four new workshops in 2010

1. Measurement of Gene Expression using Real-time Quantitative PCR
   King's College London, UK; March
2. Introduction to Molecular Techniques
   University College Cork, Republic of Ireland; April
3. Transfections and Functional Studies
   University College Cork, Republic of Ireland; April
4. Live Cell Imaging Workshop
   University of East Anglia, UK; June

For more information see our website.

www.physoc.org/education

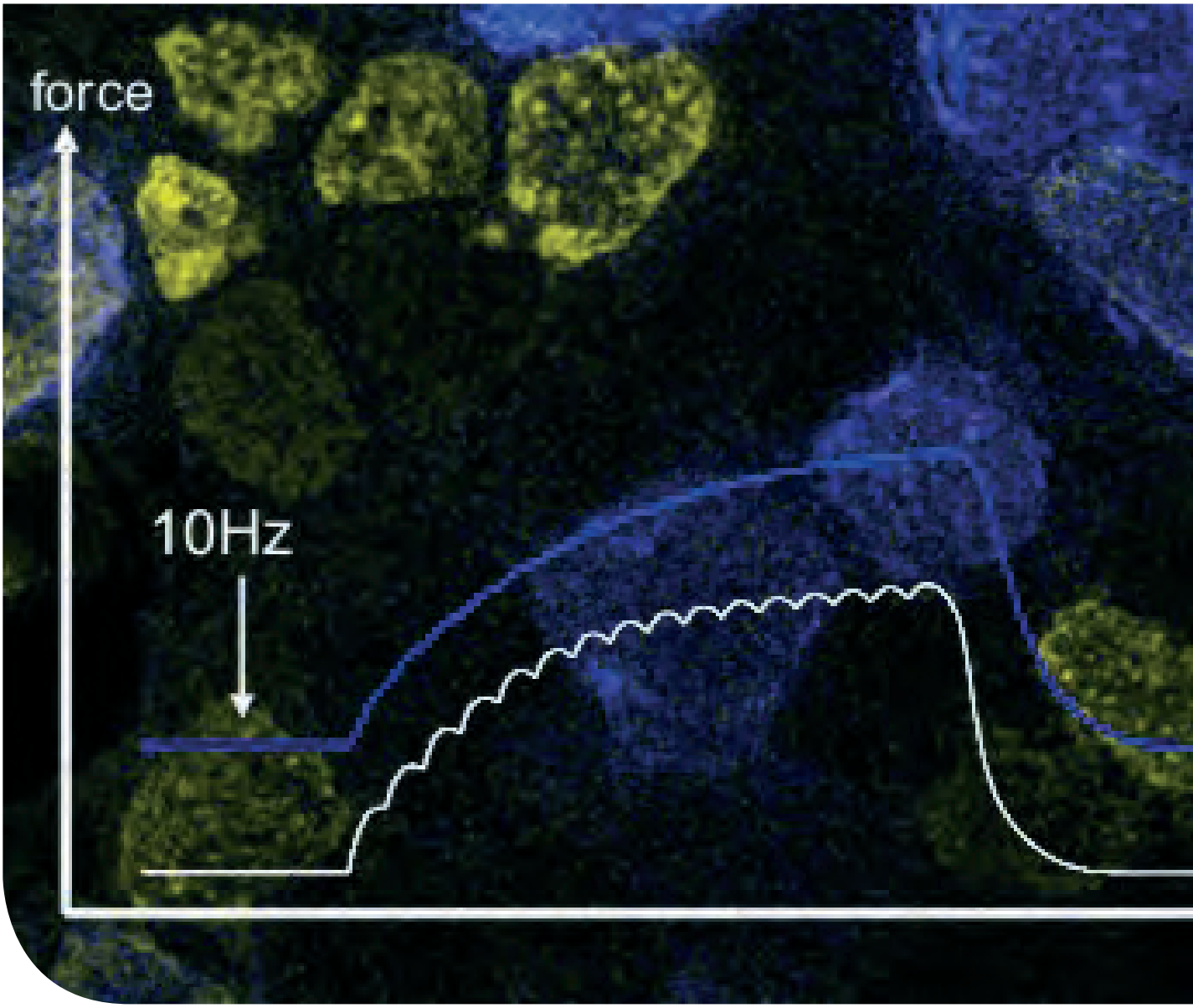


Figure from Flück (p. 28).

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