PHYSIOLOGYNEWS

winter 2006 | number 65

Meetings

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Brazil
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JOINT INTERNATIONAL MEETING WITH THE BRAZILIAN PHYSIOLOGICAL SOCIETY

Ribeirão Preto, Brazil
27-30 August 2006

For more images of Brazil, including flora and fauna, see the inside back cover

(*photos by Prem Kumar*)

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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PHYSIOLOGYNEWS

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Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Spring 2007 issue, No. 66, should reach the Publications Office (lrimmer@physoc.org) by 21 December 2006. Short news items 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 Executive Editor or a member of the Editorial Board of *Physiology News* (see contents page for details).

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Physiology News is now available on The Society's web site: http://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. In particular, 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 Executive 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 or to suggest appropriate illustrations. A photograph of the author(s) should also accompany submissions, if possible. Illustrations and photographs may be colour or black and white, prints, transparencies or tif/jpeg files with a **minimum resolution of 300 dpi**. Electronic colour figures should be saved in **CMYK mode**.

References

Authors are requested to keep the number of references to a minimum – preferably no more than two or three. Please cite all references in the style of *The Journal of Physiology* (see *Instructions to Authors 2005* at http://www.physoc.org)

In this issue

Welcome to our final *Physiology News* of 2006.

A lot of biology has to do with energy. The word 'energy' sometimes gets appropriated by pseudo-science and used for the purposes of mystification, but this should not detract from the central role of energy in science. In biological systems the conversion of energy from one form to another – e.g. chemical energy from ATP to muscle work, or to ion pumping – is a central part of what physiologists have been investigating over the last 200 years.

This issue contains a fair bit of energy. Wilfred Widdas makes a plea for more attention for surface energy as a phenomenon in Living History, while muscle, the energy-transducing machine that has fascinated physiologists perhaps more than any other, gets a good look, with four News and Views pieces and a meeting report from Heidelberg.

At this time of year the decreasing daily hours of solar energy inevitably tend to be a source of some regret. If you feel this way, perhaps the pictures from the recent meeting in tropical Brazil may cheer you up. And finally, even the sun setting (on a career) can have its upsides, as David Miller explains in his diary of a retiring physiologist.

Austin Elliott

See *Unbelievable!* (p. 50)

Homeopathic 'mumbo-jumbo'

Many scientists these days have at least the odd moment when they feel that their view of the world is under threat from a tide of what the journalist Francis Wheen, in his best-selling book, termed 'mumbo-jumbo' (1).

For scientists, 'mumbo-jumbo' manifests itself in the rejection of scientific understanding of how the physical world works in favour of mystical beliefs derived from a range of sources.

The examples are too numerous to list, but as the debate swirls it occasionally coalesces around particular issues. Recent flash-points are the challenge to evolutionary theory from so-called 'Intelligent Design' (2), and the question of whether complementary and alternative medicine has any scientific basis.

Homeopathy has recently taken centre stage in this latter debate. In May an open letter signed by 12 senior doctors and scientists (including several Physiological Society Members) urged that alternative therapies unsupported by evidence of efficacy should not be used in the NHS (3). Later, the demonstration that homeopathic pharmacies advised homeopathic formulations, which have no antimalarial action, as malaria prophylaxis garnered national media attention (4).

Following the homeopathic malaria remedy media exposé, it might be thought that the scientific absurdity of homeopathy had been clearly demonstrated. Imagine, therefore, the surprise of many scientists and doctors when the Medicines and Healthcare Products Regulatory Agency (MHRA), the body charged with controlling the safety of medicines in the UK, decided to allow homeopathic remedies to be sold with packaging featuring – for the first time in 30 years – claims about what the remedy purports to treat (5).

Previously a homeopathic remedy in a high street chemist would have been labelled '6c dilution of Gelsemium sempervirens', or something similarly obscure. It can now be sold, quite legally, as 'NoCold-Max cold and flu remedy … homeopathic'.

And as the web site of the European Council for Classical Homeopathy (6) puts it: 'To make such a claim, the manufacturers need only show that the product has been used to treat those particular conditions within the homeopathic industry.' No scientific basis. No clinical trials. No evidence of effectiveness.

The homeopaths, and the companies that produce over-the-counter homeopathic remedies, are understandably delighted.

Well, you might say, so what? The placebo effect is not new, and a fool and his/her money are soon parted. Most scientists would agree that the labelling is a joke, but in a world awash with ridiculous claims, why get worked up?

Well, firstly, perhaps, because the MHRA, acting on our behalf, is supposed to care – their web site states they 'enhance and safeguard the health of the public by ensuring that medicines and medical devices work, and are acceptably safe.' (7). How they reconcile the first part of this statement with the change in the homeopathy rules is not clear.

'The Physiological Society is concerned with the scientific investigation of how the body works … It is our view that "alternative medicine" has, with very few exceptions, no scientific foundation, either empirical or theoretical. As an extreme example, many homeopathic medicines contain no molecules of their ingredient, so they can have no effect (beyond that of a placebo). To claim otherwise it would be necessary to abandon the entire molecular basis of chemistry. The Society believes that any claim made for a medicine must be based on evidence, and that it is a duty of the regulatory authorities to ensure that this is done.'

Secondly, because – at the risk of sounding incredibly pompous – there is a principle at stake, namely that decisions of this kind should be made on the basis of scientific and medical evidence and understanding.

Finally, the MHRA's decision to allow licencing and sale of homeopathic remedies in this way is likely to be widely interpreted as approval of alternative remedies in general. This in turn will foster the perception that they work.

The Physiological Society, like other scientific societies, has been asked by the lobby group Sense About Science (5) to comment on the MHRA decision and has issued a statement reaffirming its belief in scientific evidence, and decisions based on it.

The Society's statement (box) is not, note, a blanket dismissal of all the things the public commonly regard as complementary therapies. Physiologists have long studied the effects of exercise upon the body, and the physiological actions of plant-derived substances. Work goes on into the possible physiological basis of acupuncture, or the physiological effects of alterations in diet.

But scientists want evidence, not anecdotes and hand-waving. If proper science shows real physiological effects, beyond those of a placebo compound or sham intervention, and if these can be made to work as a treatment, what you have is a therapy. Rather than being a question of 'alternative' or 'mainstream', it is down to what works – or more precisely, what we can be sure works because it can be shown to work in a properly-designed scientific experiment.

Which highlights something else we should be thinking about – our failure, as professional scientists, to inform enough of the public about what proper controls are, and exactly why some experiments are convincing, and others are not. About what the placebo effect is in medical experiments and trials. About what homeopathy actually is – you would be surprised how many people, including a good few bioscience graduates I have met, think it means 'herbal remedies' rather than 'infinitely dilute nothing' – and why it is scientifically nonsensical.

None of these is terribly complex to explain, and many of them go to the heart of what science is, and how it is done. In many ways, this seems a golden opportunity to use the public interest to put across how science offers a clear way to divide what actually works from what doesn't.

As the immortal Richard Feynman put it: 'Science is a way of trying not to fool yourself. The first principle is that you must not fool yourself, and you are the easiest person to fool.'

As this issue went to press, The Society's statement, along with many others, was being passed to interested members of the House of Lords in advance of a debate on the new homeopathy regulations on 26 October. By the time you read this, we should know if it did any good. But whatever the result, get polishing your homeopathy-debunking speech. And I like to think Feynman would not mind us pinching his lines.

Austin Elliott

1 Wheen F (2004). How mumbo-jumbo conquered the world: a short history of modern delusions. Harper Perennial.
2 http://www.royalsoc.ac.uk/news.asp?year=&id=4298
3 http://www.timesonline.co.uk/article/0,,8122-2191985,00.html
4 http://news.bbc.co.uk/2/hi/uk_news/5178488.stm
5 http://www.senseaboutscience.org.uk/index.php/site/project/86
6 http://www.homeopathy-ecch.org/
7 http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=5

New developments in stress physiology – from gene to man

A Physiological Society Focused Meeting at the University of Bristol on 4 and 5 December 2006

Stafford Lightman (above), Astrid Linthorst (right, top) and Johannes Reul (right).

The Meeting on *New developments in stress physiology – from gene to man* will provide a broad view of stress and glucocorticoid physiology from the most basic cell and molecular biology through neuronal plasticity to integrative regulation and glucocorticoid action in disease.

The first session of this Physiological Society Focused Meeting will discuss aspects of glucocorticoid – chromatin interactions, variants of the glucocorticoid receptor and interactions between the glucocorticoid receptor and MAPK and NFkB. This will be followed by a discussion of the regulation of the HPA axis at hypothalamic and higher brain levels and how targeted mutations of glucocorticoid receptors can alter feedback and, in turn, the stress response. The next session will look at the effects of stress on neuronal plasticity and include work on cell adhesion molecules, dendritic and synaptic remodelling and perinatal programming. Finally, there will be a session on glucocorticoid actions in health and disease which will cover stress, obesity, pregnancy and psychiatric disease.

In addition to the main sessions there will be oral communications from submitted abstracts whilst the other abstracts will be presented as posters.

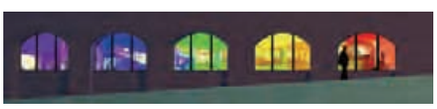
The Meeting will also host the Bayliss-Starling Prize Lecture* which will be presented by Rod Flower and introduced by Society President Ole Petersen.

The conference dinner will be aboard the historic s.s. Great Britain and we are all looking forward to and expecting a really exciting and convivial meeting.

Johannes Reul, Astrid Linthorst and Stafford Lightman
Organisers, University of Bristol, UK

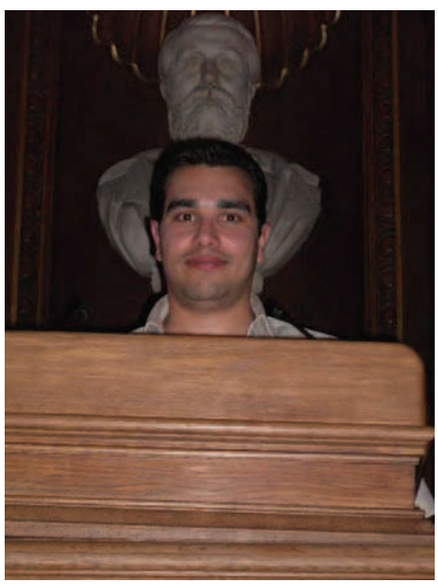
Invited speakers

Trevor K Archer
Julia Buckingham
Mary F Dallman
E Ronald de Kloet
Alison Douglas
Gordon Hager
James P Herman
Isabella Heuser
Colin Ingram
Krisztina J Kovacs
Louis J Muglia
Michael Norman
Pier Vincenzo Piazza
David Ray
Johannes M H M Reul
Benno Roozendaal
Carmen Sandi
Jonathan R Seckl
Michael G Stewart



From the top: A view of the University with the Wills Memorial Building Tower in the foreground; The Dorothy Hodgkin Building, Focused Meeting venue; SS Great Britain, venue for the Meeting dinner; Window artwork in the Dorothy Hodgkin Building.

*See Tim Biscoe's history of the Bayliss-Starling Prize Lecture on p. 39.



Control and modification of excitation-contraction coupling in healthy and diseased muscle

The Medical Biophysics Unit of the Ruprecht-Karls University of Heidelberg hosted this Physiological Society Focused Meeting on 13 September 2006. Nick Boross-Toby from The Society ensured the smooth organization together with Oliver Friedrich, Rainer Fink and Sally Davison for the hosts. The location was the splendid Alte Aula – a long, narrow high-ceilinged heavily wooded hall. Its north-south orientation with the bright sun beating on the windows meant that the late afternoon would have been very conducive to sleep were it not for some exciting selected oral presentations in the last session.

Hans Christoph Lüttgau, who had recently celebrated his 80th birthday was a guest of honour and homage was paid to him by many of the symposium speakers. It was pleasing too to have Caspar Rüegg and Reinhard Rüdel with us at the symposium.

The morning session, with Martin Schneider, Werner Melzer and Eduardo Ríos, focused on fundamental release events in skeletal muscle and elements of their control. The bottom line was that, despite huge leaps over the past few years, we still lack vital detail. After a coffee break and our first encounter with the posters in a bright and airy room, it was then back into the solemn hall. Godfrey Smith showed us that after coronary artery ligation, epicardial conduction thought the scar tissue with its surprisingly rich perfusion is essentially unchanged

Left (from top)
Time to admire the Alte Aula at the end of the day.
Charalambos Sigalas after his oral communication.
Sun beating down on the entrance to Alte Aula.
Right (from top)
Ole Nielsen with Juliet Usher-Smith, who was awarded the best poster prize.
Vincent Jacquemond (left), Peter Szentesi and Janos Almassy at lunch.
Hans Christoph Lûttgau, doyen of skeletal muscle physiologists.
George Stephenson at the poster session.
James Fraser and Gerald Elliott at lunch.

Speakers

Martin Schneider
(University of Maryland, USA)

Werner Melzer
(University of Ulm, Germany)

Eduardo Ríos
(Rush University, Chicago, USA)

Godfrey Smith
(University of Glasgow, UK)

Manuela Zaccolo
(Venetian Institute for Molecular Medicine, Italy)

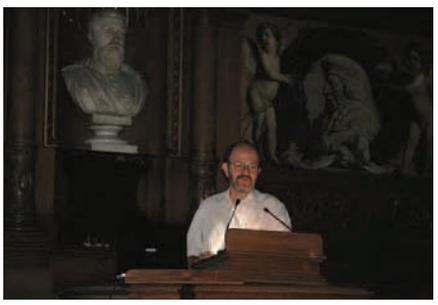
Angela Dulhunty
(Australian National University)

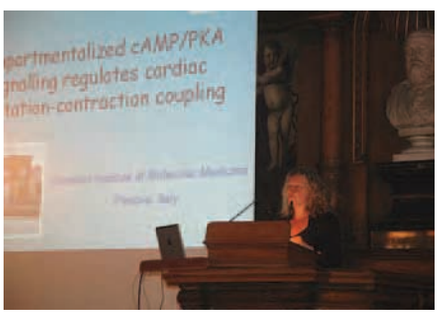
George Stephenson
(La Trobe University, Australia)

indicating that groups of myocytes presumably survive in the infarct area. Manuela Zaccolo persuasively presented evidence for the role of phosphodiesterase 2, 3 and 4 isoforms in the compartmentalization of cAMP/PKA signalling.

A surprising tasty light lunch recharged glycogen stores. The first speaker in the afternoon, Angela Dulhunty, described the consequences of the splice variants of the RYR1 and RYR2 receptors and mutations in calsequestrin on RYR opening and cellular Ca^{2+} homeostasis. George Stephenson was the final symposium speaker, and reported his recent work on the determinants of transverse tubule excitability in the mechanically skinned skeletal muscle fibre.

The final session was devoted to selected oral communications. Charalambos Sigalas told us of the complexities of calmodulin modulation of the RYR2 receptor and then Stephanie Reis reported on the subtle effects of R145G substitution in cardiac troponin I on rat cardiomyocyte contractility. Myotonia and the potential mechanisms of $[K^+]_o$ in electrical stabilization was addressed by Sunisa Chaiklieng. Ole Nielsen used the mechanically skinned rat EDL fibre to estimate the number of Na^+-K^+ pumps and maximal clearance of K^+ in the transverse tubule. The same preparation was used by Bradley Launikonis to show how store-operated Ca^{2+} homeostasis is initiated and terminated.





In between these two talks, James Fraser presented a modelling study of the determinants of sarcoplasmic reticulum electrochemical equilibria which aroused a surprisingly passionate response from the audience.

Joseph D Bruton
Karolinska Institute, Stockholm, Sweden

From the top
Inside the Alte Aula, waiting for the final session of the day to start.

Martin Schneider giving his talk (left); Eduardo Ríos answering questions after his presentation (right).

Manuela Zaccolo at the start of her talk (left); Claude Collet (left) and Bruno Allard during the coffee/poster session.

George Stephenson (left), Bradley Launikonis and Eduardo Ríos at the coffee break.

The surface energy of water from 1908

Wilfred Widdas looks back on a century of research which set him on an unfashionable path in sugar transport, and emphasises the debt we owe to physiologists

I envisaged that the surface energy of water provided the power for the working of the intra-membranous protein GLUT1. This protein was the red cell member of proteins that are now termed MFS proteins (major facultative superfamily).These membrane proteins enable water soluble molecules to cross lipid membranes. The amino acid sequence of this membrane protein was described by eight investigators in 1985 (Mueckler *et al*.). Their structure had 12 alpha helices, which they proposed spanned the lipid membrane. Several groups had proposed that the protein formed clefts which opened alternatively to the outside to allow glucose to enter and then closed behind it but opened a similar water-filled cleft to the inside, which allowed the sugar to enter from its central position in the membrane. This scheme would fit in with the carrier kinetics I advanced 50 years earlier when first studying sugar permeability at St Mary's Hospital Medical School under Professor Huggett.

Philosophically one can argue that life on this planet is supported by radiation from the sun. Short wave-length energy is used for photosynthesis to produce oxidisable chemicals from CO_2 and water. Physical chemists know that water evaporates at all temperatures but that the longer wave-length energy replaces the latent heat energy lost from the oceans by the latent heat of evaporation of water. This radiation from the sun keeps the global energy in balance as a steady state. This is important for molecules that leave the water surface and enter the atmosphere as a gas and diffuse upward being lighter than oxygen and nitrogen in the air. The water vapour condensing in the clouds may fall as rain. The rain that falls does mechanical work in eroding rocks and soil, and transfers the salts and solutes to the rivers and seas. How the same cycles of evaporation/ condensation of water can be harnessed to do effective mechanical work in cellular systems is difficult to appreciate, but my main interest has been the application of the surface energy of water derived in evaporation/ condensation cycles at submicroscopic dimensions.

Figure 1. Wilfred Widdas (right) with the late Graham Baker explaining their posters at the IUPS meeting in Glasgow, 1993.

Jumping forward nearly 50 years when working with a former PhD student at the merged Bedford and Royal Holloway colleges, a crude model of the 12 alpha helices as the membrane part of the GLUT1 protein convinced me that the scheme of working of the glucose transporter would only be possible if it was powered by the surface energy of water, which was free of metabolism but different from Gibb's free energy of proteins like ATP.

Outlining my scheme and ideas at a coffee morning break, interest was shown by all those present, and my colleague and former PhD student, Graham Baker (Fig. 1; *Physiology News* **55**, 49-50), made the most positive suggestion when he said, 'If surface energy is doing the work of transport, then we should be able to slow down glucose exits by reducing the surface tension, and we could probably do that by using alcohols since red cells can withstand high concentrations of methanol'.

The glucose exits referred to had been a form of study of human erythrocytes in a double beam photo-electric apparatus with a 25 ml cuvette that had a stirrer and 2 cm light path. Red cells incubated to hold 78-100 mM glucose when injected into glucose -free saline made their presence felt by an initial osmotic swelling, but this is rapidly followed by a linear osmotic shrinkage as the glucose is lost. That the exit is linear for over 80% of the record on a pen recorder was shown by earlier users of the apparatus. Traces in a publication by a former PhD student are shown in Fig. 2. Following Graham's suggestion, alcohols were found to equilibrate very fast and records of glucose exits were found to

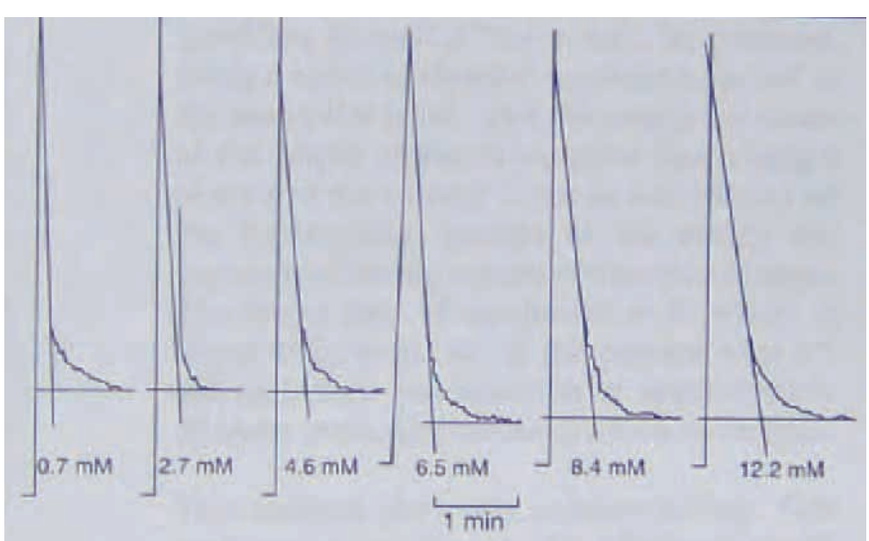


Figure 2. Linear exits of glucose from red cells with 78 mM glucose into saline's with low glucose concentrations (from Sen .& Widdas, 1962).

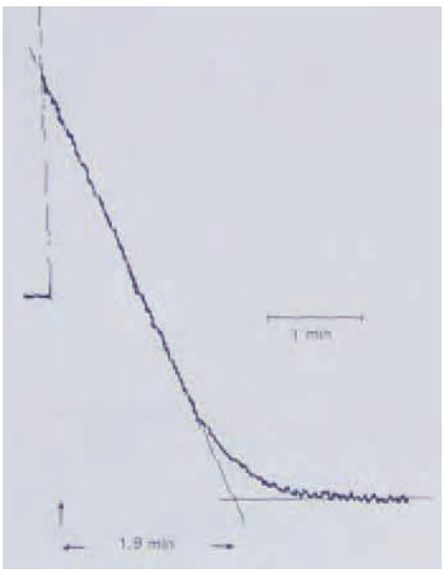


Figure 3. A tracing of a glucose exit from 100 mM glucose in 7 ½ % ethanol (2.28 M), which is four fold isotonic concentration but is rapidly equilibrated to give a linear 67% inhibited exit (from Widdas & Baker, 1991).

Table 2 Half-inhibitory concentrations of the four monohydric alcohols at 28°C

Alcohol	Inhibition (50%) (molar)	Traube's rule
Methanol	1.88	1.88
Ethanol	0.71	1/3 = 0.63
Propanol	0.26	1/9 = 0.21
Butanol	0.069	1/27 = 0.070

Traube's rule states that as one ascends a given homologous series 'each member is about three times more effective in lowering the surface tension than its immediate predecessor' (Traube, 1891; quoted by Findlay, 1944).

Figure 4. A copy of the Table 2 taken from the same 1991 reference. This table records the concentration for 50 % inhibition of glucose exit (by lowering of the surface tension) and the approximation to Traube's Rule. A recent but second application of these alcohols to biological studies (Ly & Longo, 2004) has also given reductions in surface energy according to Traube's Rule.

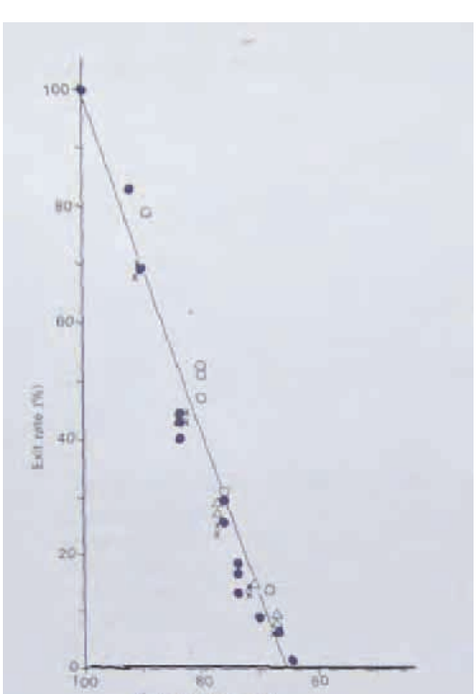


Figure 5. The linear fall of glucose exit rates as a percentage of the maximal rate (100%) plotted against the surface tension of the saline relative to normal water (100%).

be just as linear. An example with ethanol at 7.5% is shown in Fig. 3. The inhibitory effect of alcohols was readily measured.

Soon after this we started on the experiments that Graham had suggested and found that the other lower alcohols reduced both the surface tension and inhibited glucose exit rates at even smaller concentrations than methanol. In the course of these studies, the four alcohols inhibited the glucose exits to 50% in concentrations that progressively reduced (Fig. 4). This almost threefold reduction in concentration was in accord with a physical chemistry phenomenon, which was discovered by Traube in 1891 and is known as Traube's Rule (Findlay, 1944)

The linear fall in glucose exit rate with the percentage fall in surface tension from 100% to 65% of that of water, and the fit of the 50% inhibition values to Traube's rule, were both pointers to the involvement of the surface energy of water as suggested from the knowledge of physical chemistry (Fig. 5). Further, we found that the proposal for the involvement of surface tension of water in biological functions was not original. Czapek, a botanist from Jena had reported in 1911 that he had found that plants were not viable if the surface tension was reduced to 68% that of normal water. This toxic value of lowered surface tension (68%) corresponded closely to the cut off value (65%) for glucose exits. The experimental results were reported to The Physiological Society in two pre-circulated communications at the 1990 Bristol Meeting. One was given by Graham Baker and I presented the other. Both were approved, but a longer paper was rejected by two journals and only published over a year later by a less well known journal whose Advisory Editor was our Professor of Physical Chemistry (Widdas & Baker, 1991).

However, the structural model of the opening and closing cleft mechanism involved the breaking of the water channel to the liquid water at the centre, firstly from the outside (after the sugar had diffused into the centre from the outside bulk water). The separation

allowed an outer bolus of water to be expelled and the cleft at this side closed. As spherical glucose sugar was now in the centre, the 12 alpha helices were regarded as being semi-rigid and behaving like planks on a child's seesaw. They closed around the glucose like they would around a fulcrum, and this opened the cleft on the inside as a near vacuum.

The opening as a near vacuum is due to two physical chemical principles, which few understand. The first is that the mouth of the inside cleft is far too small to admit liquid water, which would need Laplace's pressure ($P = 2\lambda/r$) and this would be over 2,000 atmospheres for a radius in the nm dimensions. Consequently the water forms a plane surface across the mouth of the conical cleft. This is also seen in umbrellas where the fabric is full of small holes but the penetration of water does not occur because of surface tension. The second principle is that a plane surface of water exposed either to air or to a vacuum space is a liquid surface from which individual water molecules can leave by evaporation. The water vapour enters the cleft where it can condense on polar groups or on water molecules already present.

The change from liquid to gas is a change of state needing 540 calories per gram. It is difficult to visualise the enormous amount of extra energy which is hidden away as latent (hidden) energy in liquid water. The physical chemists sometimes refer to this as mechanical energy since it is the only part of the surface energy of water that can do mechanical work (Widdas, 1993). The First Law of Thermodynamics explains how all forms of energy have a heat equivalent, but the reverse is not true. A source of heat energy is not an explanation of how work is done. To perform work an 'engine' or 'engine-equivalent' is required to convert the energy source into meaningful or purposeful movements, or into some other form of work.

In the case of work from surface energy of water it is found that if you have an 'engine' the magnitude of work possible is proportional to the area of water surface eliminated multiplied by the value of the energy content per unit area. For water this latter value is already well known as 73×10^{-3} Jm^{-2}. In the membrane transporter for glucose, the breaking of the continuous water channel needs energy to create two half spheres for the two new ends of water. Two halves are a whole, so knowing the radius, the total area is $4\pi r^2$; and the energy is easily put into heat quantities, or joules. When this was done it was found that having measured the turnover rate radioactively, and also the number of transporters in each red blood cell, it was possible to determine the total mechanical work being done by the glucose transporters in 5 litres of blood every minute. The value was more than 10 times that of the resting metabolism for an adult of 70 kg.

This unexpected and surprising result of physical chemical calculations had several philosophical implications. Firstly, it was impossible to imagine that this amount of work free of oxidative metabolism was provided only for the membrane transport of glucose. During the long epochs of evolution nature would have found more widespread uses for the work potential of the surface energy of water. Work production is largest in muscles, which are naturally considered for a system where the surface energy of water might be used. This had already been proposed by Bernstein (1908) almost 100 years ago.

However, the provision of heat energy is not enough to explain mechanical work and therefore a description of the muscle 'engine' was looked for in the literature, but found to be lacking. The reason for the failure, is seen as the attempts to explain the muscle contraction mechanism entirely from one energy source, namely that of ATP hydrolysis whereas the surface energy of water was readily available as a second energy source to supplement the ATP energy source. To provide a scheme employing two energy sources in place of only one is much easier and a paper proposing this was submitted to *Experimental Physiology* but was rejected as being unsuitable at this time given its particular focus.

Thus, not only has the surface energy of water not been accepted as explaining the working of the glucose transporter protein in erythrocytes for the last 17 years, but its supplementation of the ATP-hydrolysis in muscle contraction, suggested by Widdas & Baker in 2001 and again in 2004, is also ignored and unacceptable to the established scientific opinions.

The modern interest in genetics has many examples where we find clefts too small to admit liquid water but involving detailed reactions that need a watery base. Their source of energy to do detailed work outlined by earlier microscopists is never explained, but is presumed to follow from the structural detail published by Watson and Crick (1953). Novel proteins are synthesised from changes in DNA as part of complicated chemical changes that clearly need more than simple thermal vibrations but without the work involved being fully explained.

If in future investigations physical chemists take more interest in biological functions, studies of the surface energy of water will feature more strongly in the next decades of the 21st century.

Wilfred F Widdas
Honorary Member, Lincolnshire, UK

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Wilfred Widdas recalls:

My entry to the London physiology scene came just after World War Two, 9 years after I had qualified as a doctor. Following 1 year in general practice, I had spent seven and a half years in the Royal Army Medical Corps, being released with the honorary rank of Major. Seeking a post-War job in science, I was rejected by the Secretary of the MRC and the Head of the National Institute for Medical Research at Mill Hill. Professor Jo Bernal, the Government adviser in physical research, could only offer me a sociology job, living in a new town and reporting on how the East Enders adjusted to living in their new environment – at least, that was how I interpreted it. It was quite opposite to my ideas of scientific research work, though, so I declined.

After some other unsuitable options, I was lucky to get one of five postgraduate scholarships offered by St Mary's Hospital Medical School for ex-service doctors and started to work under Professor A St G Huggett, later FRS. These scholarships were worth £500 per year, much less than my army salary had been but the grant was free of tax. I accepted the effective 10 years 'juniority' relative to the other normal research students for 3 years before being given a lectureship.

Huggett had come from Leeds as professor, and brought with him his chief technician Mr Hancock – in my opinion the best physiological technician in London at the time. A V Hill's chief technician, Mr Parkinson, who was the expert at making the special thermocouples for A V's research, was also very good and was the only one of Hill's Department whom I knew well. Parkinson and I shared collecting Government surplus apparatus for research after the cessation of hostilities. We had to visit empty RAF hangars where equipment would be displayed for sale to 'junk shops' in Tottenham Court Road. Luckily, universities had a special 'first chance' to buy. I got an ink-writing pen recording milliammeter, which I used for many years.

At St Mary's the research was centred on fetal physiology – copied from Huggett by Sir Joseph Barcroft at Cambridge as a wider study. The interesting fact that set me on a path in sugar transport was that maternal sheep only had glucose in their blood, whereas the sheep fetus (the unborn lamb) had glucose and fructose in its blood, so that its blood sugar was higher than its mother's. I was able to show from the results of Huggett and his biochemist, Warren, that the glucose could not cross the placenta by simple diffusion (as stated in the most prestigious – American – biochemistry textbook of the day, but must come across by a special 'carrier' mechanism.

The mathematics I used were beyond Huggett's mathematical expertise, so he sent my calculations to A V Hill for advice. As I remember, Hill replied that it was outside his field but he had been advised by his biochemist colleague, E J Harris, that diffusion could be the explanation and therefore recommended rejection of my approach. I was too junior to engage Hill any further and did not obtain Harris' explanation as to how diffusion could explain the concentrations I had used in my analysis.

Although I cannot remember the exact dates (these Living History articles often start 'I clearly remember' – for myself this would be impossible. My memory is good for some items but for others it has gone, and time scale in particular is often far from clear. Perhaps from the perspective of 90+ years precise dates are not so important!), this must have delayed me by about 2 years until I found that R B Fisher and Parsons, biochemists at Oxford, were using the same formulae as I had used for glucose transport in other situations. So I presented two papers in the early 1950s.

When I had collected data from my own blood as well as that of fetal cells, I wrote a PhD thesis. Huggett got Professor F J W Roughton of Cambridge to act as external examiner. At the interview, I recall that Roughtson said, 'Widdas, I have read through your thesis and recalculated all the equations in it. I found them all correct. But … (he paused, and you can imagine my anxiety rising), then he continued 'but, I found three sentences without a verb in them.' Professor Roughton, FRS, had hit on a weakness I have admitted since school days and now I usually get a relative with a BA in English Literature, or similar, to read my papers (presently this is my grand-daughter who has a BA from Lancaster University).

An (endless?) summer in the life of a retiring physiologist

David Miller enjoys the nostalgia and rewards of an early retirement from university life

As with my predecessors in this series, this is weeks/months/summers rather than *A day in the life of*... To set the scene, this spring I took the too-tempting early retirement deal from Glasgow University; my transitional state is my introspective preoccupation.

In late April came the standard retirement 'do'. (I'd *started* at Glasgow on 1 April 1977 but – to paraphrase The Who – wouldn't get fooled again by *leaving* on the 1 April too). In my case, the 'do' included a valedictory seminar and a late afternoon gathering of colleagues, with several surprise visitors, then speeches and many 'farewells' gratefully received. Fellow retirees will recognise the growing sense I had of being at my own funeral as the unjustified words of praise and thanks were heaped up.

The rites of passage to retirement have continued since then with clearing my office and downsizing the lab. This process (ongoing) generated dozens of bags of confidential waste, general waste, recycling waste and a long 'help-yourself' bookshelf for bibliophile colleagues to plunder. However, I still wrestle with one widespread problem; how to deal with 80 shelf–feet of *The Journal of Physiology*? I have a run from 1961 to date, the volumes prior to 1978

Figure 1 (above). Hunter's Moon in Torshavn harbour, June 2006.
Figure 2 (below(). Neil Spurway and David Miller moored at Midvagur, Faroes.

'inherited' from my late colleague Oliver Holmes. Tilly Tansey, at the Wellcome Trust, told me that even the *complete J Physiol* she assembled for the digitising project could not be found a home, so I despair of 'saving' my modest sub-set. Debating the merits of print browsing *versus* the oxymoronic, electronic 'internet browsing' is for another place.

My clear-out also fuelled a powerful surge of nostalgia. I was sharply reminded of many past colleagues, of students (undergrad and postgrad), some active and prominent in physiology, some in medicine (i.e. applied physiology), others hardly ever heard from, or of, since. I recalled Reg Chapman's remark to me on completion of my own thesis that 'he had now replaced himself, so his job was done'. (However, like many supervisors, Reg didn't stop after his first scientific 'child'. Just what *is* a reasonable number for one's scientific progeny?)

Stimulated by reading some of the old exam papers, lecture notes, and committee papers that choked office and lab, I was driven to ponder the changes wrought on our science and university education. If *you* have any to hand, do glance at some 1970s, 80s and 90s past exam papers. They will surely reveal the 'dumbing down' that 30 years (or more) have wrought. Notwithstanding the broader curriculum that many courses have deliberately adopted, the intellectual pitch has declined. The best students *do* remain excellent but the *range* of student attainment is much wider now so median standards are surely lower. Yet, paradoxically, median 'grades' are higher. Ponder the standard of Honours research projects. While (mere) technical sophistication rises steadily, the aspiration to novelty and

thoroughness seems much lower. Assuming the experiments work, the ease with which data can be collected, analysed and presented now is stunning compared with what earlier decades allowed. Yet the conversion of data into results and the quality of the final output seems not to match the new tools available. Do you detect a whiff of the disenchantment that contributed to my early retirement decision?

Amongst special trophies that my clear-out has generated, the nostalgia wave rose high as I chanced upon delights such as: log and trig tables, the 'Rubber' Handbook, my Castell 'engineering' slide rule, three cycle log graph paper, 5.25" floppy discs, a Sinclair programmable calculator owner's manual, Letraset, and much more. I have now ceremonially handed over my cherished box of fine Allan keys to Godfrey Smith's safe hands. He is one of a dwindling group who knows what they are and has good uses for them. But, despite a ruthless clear-out, the 'bottom drawer' is still full of results to be written up, biographical notes on Sydney Ringer and more, plus I have the stimulation of my membership of The Society's History and Archives Committee to help to fill my days from here on. And my wife, Carolyn, has 'a list'.

Amongst the responsibilities that I have passed on, one concerns the advent of 'electronic' PhD theses. My last 5 years involved postgraduate administrative matters as head of the Faculty Graduate School. This led me to be volunteered as the sole academic on the steering group of EThOs (Electronic Theses Online), a national project concerned with making theses searchable and accessible on line.* I raised there the concerns about shared intellectual property, plagiarism, self-censorship and priority that, if neglected, will dog this otherwise laudable aspiration. At root, a profound reappraisal of the very nature of the UK PhD thesis, never mind the training and education of the PhD itself, seems long overdue.

On an entirely happy note, my personal transition from 'work' to 'play' was marked by a wonderful opportunity. I was available *in June* to crew for my long-time Glasgow colleague Neil Spurway, sailing to the Faroes in his 31-foot boat Hunter's Moon (Figure 1 and 2). I joined Neil in Orkney. Fortuitous timing saw a day as an External Examiner for the Aberdeen medics end for me at the harbour, rather than the railway station, as I boarded the ferry to Kirkwall. Over the next week, Neil and I sailed, with sight-seeing interruptions, through Orkney to Fair Isle (which lived up to its name) and thence to Shetland. A few days there set us up for the near–200 mile passage from Ronas Voe (NW Shetland) to Torshavn (the Faroes' capital). We completed the run in about 34 hours, almost entirely on one tack thanks to a remarkably steady, if at times uncomfortably strong, south-westerly wind, emboldened by the reassuring 'advice' of GPS. I stayed a further week aboard as we explored much of what this unique Atlantic archipelago has to offer (except Guillemot, which despite the 600,000 nesting pairs available, was unaccountably 'off' one restaurant's menu that week). So what do *you* know of the Faroese Nobel Prize winner for Physiology Niels R Finsen? (For me, the return journey was a simple 1 hour flight. Neil S made it safely back and still afloat, if not entirely without incident, some days later).

My 'real' summer holiday was to NE Spain and SW France, and it did prompt one physiological train of thought. Might the acclimatisation to higher temperatures on the Med, the attendant dehydration and my raised daily alcohol intake be associated? A significant proportion of alcohol dehydrogenase activity is inducible and alcohol is a diuretic: could the acceleration of C_2H_5OH breakdown as a holiday proceeds be a major contribution to reduced diuresis and thus 'rehydration'? I reckon after 2 weeks I'm usually just about equilibrated. If anyone has acted as an alcohol-free control for this phenomenon, do let me know.

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*http://www.gla.ac.uk/ibls/NBS/nbsstaff/djmiller/etheses.rtf

Research unveiled at The Physiological Society's Main Meeting held at University College London from 4 to 7 July 2006

Obesity risk for children can be traced to a mother's diet

New research, funded by the EU's early nutrition programming project, reveals that a mother's intake of a high fat diet during pregnancy could lead to persistent changes in a child's bodyweight leading to obesity in adulthood. The research, carried out by Anne-Maj Samuelsson (Division of Reproduction and Endocrinology, King's College London), investigated the mechanisms whereby a mother's diet influences the offspring. The research reveals that a mother's intake of a fat-rich diet during pregnancy is more likely to produce offspring with increased fat stores due to enlarged fat cells, altered fat metabolism, and higher lipid level in their blood.

The tight-fit brain – study reveals brain swelling as a cause of migraine headaches

The secrets of migraine headaches may lie in acute mountain sickness where brain swelling as a result of lack of oxygen causes severe headache and vegetative symptoms. The challenge associated with understanding headaches is that academics usually study the symptoms once they have formed. Research led by Damian Bailey (University of Glamorgan) highlighted for the first time what happens during the evolution of a headache. Volunteers were exposed to lack of oxygen in a simulated high altitude chamber, to investigate the build up to, and wind down from, the resulting headaches. Under these conditions (at a simulated altitude of 4,600m), half of the subjects typically developed symptoms that were indistinguishable from a migraine.

Heat halts pain inside the body

Brian King (UCL) led research that found the molecular basis for the long-standing theory that heat, such as that from a hot-water bottle applied to the skin, provides relief from internal pains, such as stomach aches, for up to an hour. The team found that the heat receptor, known as TRPV1, can block P2X3 pain receptors, thus stopping the pain being sensed by the body.

More information at http://www.physoc.org (News and Events)

What structures bear the tension and store energy in lengthening muscle?

When active muscles are stretched the cross-bridge cycle is truncated by suppressing the power stroke and thereby reducing ATP consumption; the high tension they exert is generated by stretch-induced strain in the pre-stroke cross-bridges. Other, non-crossbridge, structures also make a substantial contribution to tension and energy storage

Textbooks of physiology often give the impression that when muscles are activated to produce tension, they either shorten performing work or remain at constant length if restrained by a suitable load or antagonistic muscle (isometric contraction). Yet, stretch of an active muscle, somewhat confusingly referred to as an eccentric contraction, occurs frequently during daily activities. Examples include the lengthening of the biceps when lowering a heavy weight, or of the calf muscles when walking downstairs. Lengthening contractions may also serve as a braking mechanism to decelerate the body when running downhill or landing from a jump. Lengthening muscles also store energy which may be used during a subsequent shortening contraction to enhance the tension produced; this phenomenon is the underlying basis of plyometric exercise-training. Yet our understanding of the molecular processes involved in lengthening has been unclear.

Gerald Offer (left), KW Ranatunga and Gavin Pinniger.

An active muscle strongly resists being stretched, developing up to twice the isometric tension. Yet the consumption of the fuel, ATP, and hence the energy output (heat plus work) declines. What is the molecular explanation for this seeming paradox? It will be recalled that the structural basis of muscle contraction is the cross-bridge cycle, the interaction of heads of the myosin molecules (M) of the thick filaments with actin (A) filaments. The Lymn-Taylor scheme summarises the main events in this cycle (Fig. 1A). Hydrolysis of ATP occurs on myosin heads detached from actin (step 1). The heads carrying the products of hydrolysis, ADP and Pi, then attach to actin (step 2). Tension is generated by a power stroke, a conformational change in the myosin head, associated with release of Pi (step 3). Detachment of post-stroke heads, after they have lost ADP and rebound ATP, completes the cycle (step 4). How does this cross-bridge cycle adapt to lengthening? Since the power stroke generates force, it is strain-sensitive and hence it is expected to be slowed by the increased strain on the heads caused by the lengthening.

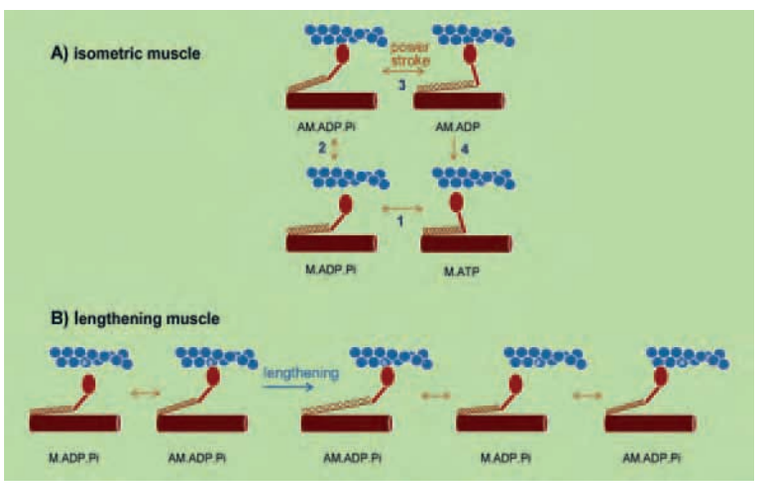

Figure 1. Lymn-Taylor cross-bridge cycle and its truncation during lengthening
A, In isometric muscle: Step 1 is ATP hydrolysis on the detached heads, step 2 is the attachment of myosin heads to actin or their detachment; step 3 is the power stroke (or its reversal) involving the swing of the lever arm of the myosin head; and step 4 is the irreversible step. Note that in isometric muscle the filament positions remain the same and force is generated by the power stroke which stretches the elastic element, here schematically represented by a spring connecting the myosin head with the thick filament backbone.
B, During lengthening: The pre-stroke heads initially attach to the actin subunit marked with an asterix. The movement of the actin filament from left to right stretches the spring increasing the force and the heads detach at high strain. They reattach at an actin subunit further from the Z-disc and the process is repeated.

So a simple explanation for the reduction of ATP consumption in lengthening muscle is that the cross-bridge cycle is truncated, the power-stroke and subsequent detachment of post-stroke heads being increasingly shut down as the lengthening velocity is increased. But if the power stroke rate is reduced, how do we account for the increased tension exhibited during lengthening? The pre-stroke heads that attach to actin, given a sufficient lifetime, will be dragged to higher strains and this will produce force; the heads will eventually detach when highly strained and reattach to actin subunits further away from the Z-disc (Lombardi & Piazzesi, 1990; Fig. 1B). It had been supposed that a special mechanism (forcible detachment) might operate when tension prised the pre-stroke heads off the actin but it is now appreciated that when force is applied to a complex of two proteins, it merely enhances the spontaneous rate of dissociation. So tension can be generated during lengthening without the power stroke, the high force being borne by pre-stroke, rather than post-stroke heads (Getz et al. 1998; Pinniger et al. 2006). Our computer simulations of active muscle based on the Lymn-Taylor scheme are able to account for the lengthening limb, as well as the shortening limb, of the force-velocity relation without the need to postulate extra intermediates in the cross-bridge cycle.

So far we have discussed only the contribution that cross-bridges make to tension. But there are strong indications that other, non-crossbridge, structures also contribute (Edman & Tsuchiya, 1996). For example, during lengthening, when work is done on the muscle, much of the energy absorption cannot be explained simply by the enhanced cross-bridge strain (Linari *et al*. 2003). Two further indications are shown by the tension responses during and after the application of a constant velocity stretch to a bundle of isometrically contracting muscle fibres (Fig. 2). There is an initial rapid phase of tension rise due to the cross-bridges being increasingly strained, interrupted early on by a small but detectable dip in tension as the post-stroke heads undergo the reverse power stroke. There is then a marked reduction in the rate of tension rise (Fig 2B); simulations suggest that this transition (indicated by the arrow in Fig. 2B) is due to the cross-bridges approaching the new steady-state truncated cycle (Fig. 1B). However, the tension continues to rise slowly thereafter to the end of the stretch. After the stretch, tension decays to a level which is higher than the isometric tension.

Both this continuing slow tension rise after the transition and this residual force enhancement are hard to explain on the basis of cross-bridges acting alone and have been attributed to a non-cross-bridge component. The peak tension increases with velocity of stretch to a plateau of about twice the isometric force, whereas the residual force enhancement remains the same irrespective of velocity. Figure 2C illustrates the velocity dependence of the contribution to tension by cross-bridges (measured by the tension at the transition) and the contribution by non-cross-bridge elements. The cross-bridge tension rises steeply to a plateau 60% higher than the isometric force at high velocity, whereas the non-cross-bridge tension is insensitive to velocity. Two further findings support the existence of these two tension components. Firstly, the tension decay after ramp stretch also shows fast and slow phases. Secondly, when active muscle force is drastically reduced by a specific myosin-crossbridge inhibitor

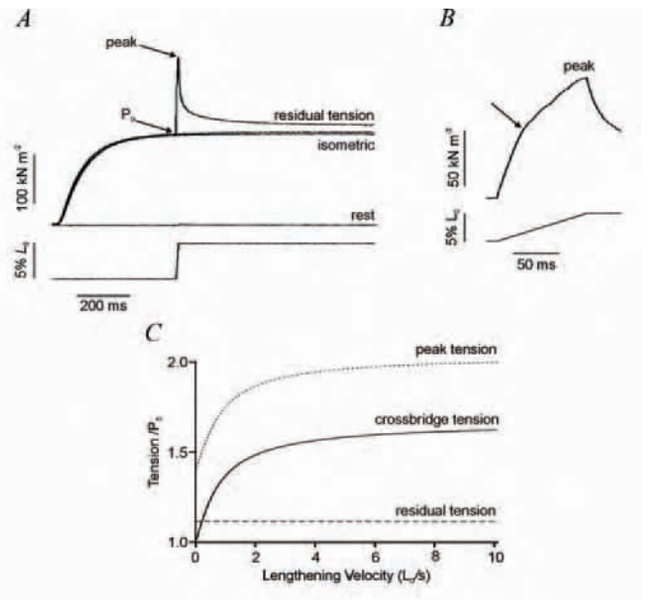

Figure 2. Tension responses to stretch and contribution of cross-bridges and non-crossbridges to tension

A, Tension response (upper trace) from a rat fibre bundle to a 5% ramp stretch (lower trace) applied on the plateau of an isometric tetanic contraction. Also shown are two isometric contractions, one at the initial length and the other at the extended length, and the tension response in resting muscle.

B, Tension response at an expanded time scale to show the change in slope on the tension rise (denoted by arrow).

C, The effect of velocity on the peak tension, the contribution to the peak tension by cross-bridges and the residual tension. The non-crossbridge tension is the difference between the peak tension and the crossbridge tension.

(BTS), the rapid phase of tension rise during stretch and the fast phase of tension decay afterwards are greatly diminished, whereas the slow phases of tension rise and decay and the residual force remain high (Pinniger et al. 2006). Our interpretation is that non-cross-bridge structural elements stiffen on activation and provide a tension that increases progressively throughout the stretch. The peak tension thus has contributions from both cross-bridge and non-crossbridge elements; the residual force enhancement arises from a partially decayed non-crossbridge force.

The residual force enhancement and continued slow tension rise during a stretch had been attributed to sarcomere inhomogeneity and sarcomere popping, uncontrolled elongation of sarcomeres. However, no convincing direct evidence of sarcomere popping has been observed experimentally and, tellingly, no popping is observed when active myofibrils are stretched even though their tension response to stretch shows the above features (Telley *et al*. 2006). Our proposition is that interactions between actin and the titin filaments that connect thick filaments to the Z-disc, or between actin and C-protein (an accessory protein of thick filaments) are recruited by the release of Ca^{2+} on activation and play a significant role in energy storage.

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Acidification protects skeletal muscle volume during anaerobic exercise

Biophysical measurements and theoretical modelling of resting skeletal muscle exposed to extracellular lactate demonstrate that intracellular buffering of hydrogen ions precisely offsets the effect of increased intracellular lactate on cell volume

Muscle exercise has long been associated with the transmembrane entry of water and an accompanying cell swelling (Kjellmer, 1964; Lannergren, 1990). Although it is now generally accepted that this water movement is the result of an increase in intracellular osmolarity (Ward *et al.* 1996), the precise origin and nature of this increase in osmolarity is not well understood. One candidate often implicated is the intracellular lactate produced during anaerobic metabolism. However, lactate accumulation is then accompanied by production of H^+ ions from the hydrolysis of ATP and recent charge-difference modelling of skeletal muscle electrophysiology (Fraser & Huang, 2004), which suggested that steady state cell volume is determined principally by the intracellular membrane-impermeant anion content and its mean charge valency, predicted that cellular acidification would produce quantifiable reductions in cell volume through the association of H^+ ions with these impermeant anions. This hypothesis was subsequently confirmed when experiments producing intracellular acidification in amphibian muscle through addition and subsequent withdrawal of NH_4Cl from the extracellular solution (Fraser *et al.* 2005) produced predictable decreases in cell volume that were proportionate to the increase in intracellular $[H^+]$. This suggests a mechanism by which cell volume could be conserved in the face of the production of lactate and H^+ during anaerobic exercise. Thus, whilst the additional lactate would increase the intracellular osmolarity and so tend to *increase* cell volume, the accompanying acidification would be expected to *reduce* cell volume. The consequent steady-state volume would then depend on the balance between these two opposing effects.

Our study (Usher-Smith *et al.* 2006) establishes that, in fast-twitch amphibian muscle, these two effects precisely balance each other. By

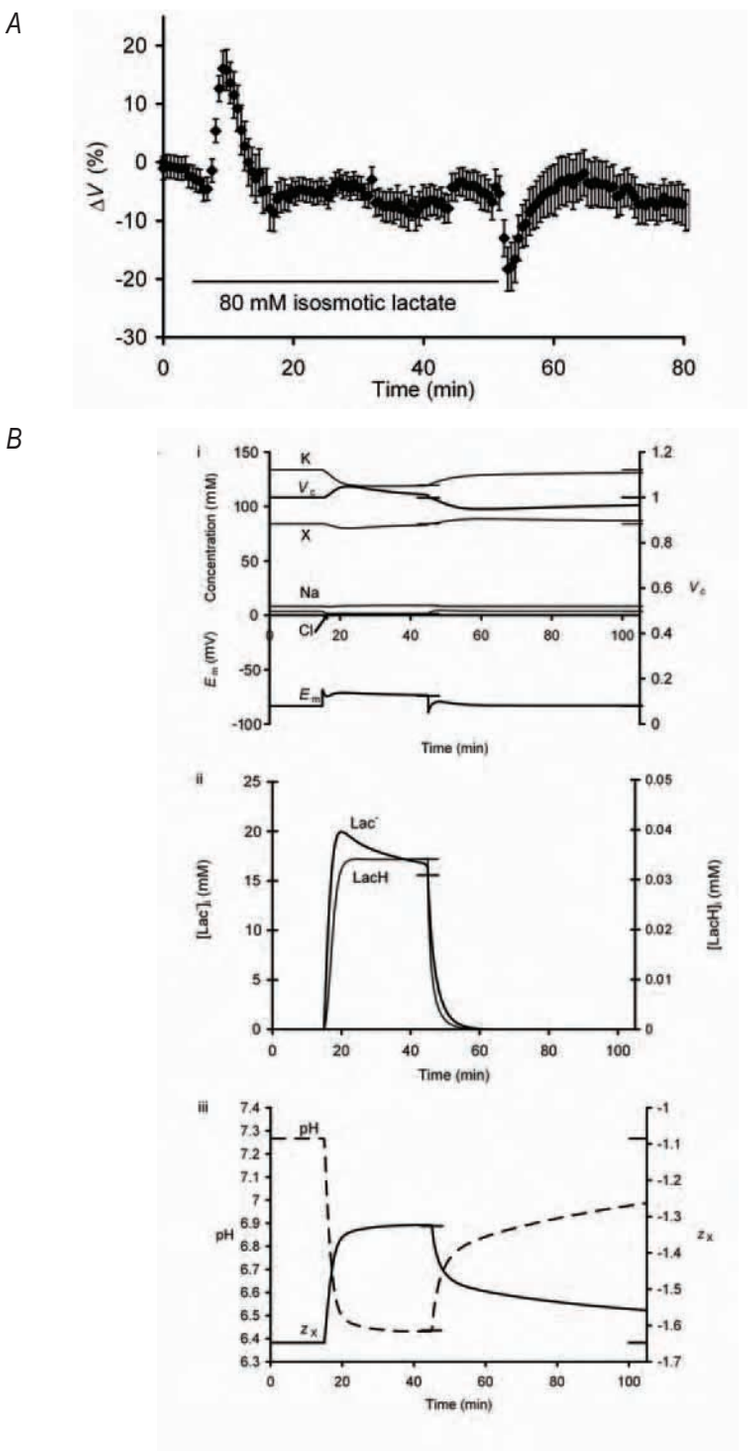


Figure 1. *A,* Plot of the mean cell volume change, ΔV_c, (± S.E.M, n = 6) against time during and following exposure to an isosmotic solution containing 80 mM lactate. *B,* Charge-difference modelling of the addition at 15 min and withdrawal at 45 min of isosmotic 80 mM lactate Ringer solution from a model cell initially at steady state in normal Ringer solution. Horizontal bars at 45 min show the final steady-state values of each modelled variable after more extended exposures to lactate-containing solutions, while horizontal bars from 100 min similarly denote final values after extended periods of recovery in normal Ringer solution. Thus charge-difference modelling predicted that lactate addition and withdrawal would cause minimal volume change, despite an increase of $[lactate^-]_i$ to >15 mM during the lactate loading phase, in accordance with the experimental results depicted in *A*.

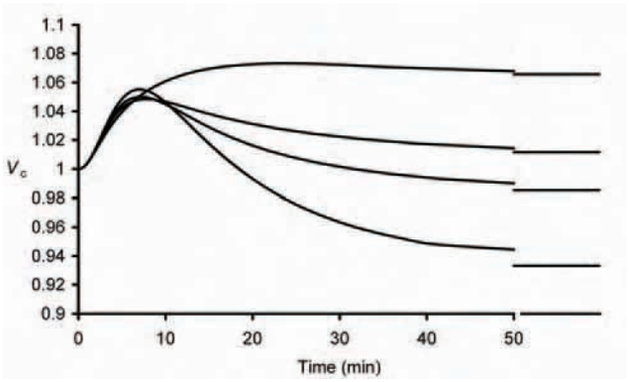
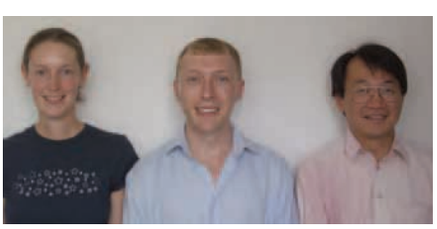


Figure 2. Charge-difference modelling of volume changes over time during exposure to isosmotic 80 mM lactate Ringer for cells with intracellular buffering capacities of (from top down) 0.5, 0.9, 1.1 and 1.5 times normal. Horizontal bars plotted past 50 min show final stable steady state values of V_c in each case.

exposing resting frog muscle to extracellular solutions containing lactate we were able to reproduce the increases in intracellular lactate and H^+ observed following exercise whilst avoiding the wide range of other metabolic and osmotic alterations which occur during exercise. An integration of the results from a range of experimental and theoretical techniques then enabled us to quantitatively examine the combined effects of these increases in lactate and H^+ on cell volume.

By using ^{1}H-NMR to compare the intracellular lactate concentration, $[lactate]_i$, resulting from exposure to extracellular lactate at a range of concentrations with that following low-frequency electrical fatiguing stimulation, we successfully developed a protocol that increased $[lactate]_i$ in resting muscles to levels close to those following fatigue. Corresponding measurements of intracellular pH, pH_i, using pH-sensitive microelectrodes similarly confirmed that the pH_i in these resting muscles was within the range previously recorded in fatigued amphibian muscle. Relative cell volume was then measured using confocal *xz*-plane scanning during and after exposure of resting fibres to lactate (Fig. 1A). Addition of extracellular lactate produced an initial increase in cell volume but this swelling was short-lived and, whilst still exposed to solutions containing lactate, the cell volume returned to its control value. Isolated increases in intracellular lactate and H^+ to levels comparable with those observed following stimulation do not, therefore, significantly alter steady-state cell volume.



Juliet Usher-Smith (left), James Fraser and Christopher Huang.

A modified charge difference model of the quantitative relationship between volume and membrane potential developed by Fraser and Huang (2004) then combined these individual cellular observations to reconstruct the osmotic and electrophysiological workings of the cellular system as a whole. In agreement with the experimental findings, simulated addition of extracellular lactate produced intracellular lactate accumulation, cellular acidification and a transient volume increase followed by recovery of the volume to initial resting values (Fig. 1B). It also clarified the mechanism responsible for these volume changes. The initial increase in cell volume could be attributed to a rapid entry of lactate and resultant increase in intracellular osmolarity but, as the pH subsequently decreases and H^+ ions bind to negatively charged sites on intracellular membrane-impermeant anions, the charge on those anions, z_x, becomes less negative. This results in a decrease in the net intracellular anionic charge and so allows potassium, the predominant intracellular cation, to leave the cell, reducing the intracellular osmolarity and returning the cell volume towards control values.

This close agreement between experimental and theoretical results additionally prompted an extension of the model to allow analysis of cellular parameters not directly amenable to experimental study but nevertheless important to the mechanisms underlying these adjustments. For example, it was possible to examine the effect of variations in total intracellular buffering capacity on the volume changes (Fig. 2). This showed that, as expected, the small initial volume increase observed on exposure to extracellular lactate is not affected but the final steady state volume is profoundly influenced by the relative intracellular buffering capacity: addition of lactate and H^+ to a cell in which pH_i has no influence on cell volume due to a relative buffering capacity of zero produces a 13% volume increase whilst 80 mM extracellular lactate would be expected to produce a 7% volume decrease if intracellular buffering capacity was increased by a factor of 1.5. It is only with buffering capacities similar to those actually measured in frog muscle that the final volume is not significantly different to control values as seen experimentally.

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Did evolution go the wrong path for the human lung?

Birds and mammals evolved along two separate evolutionary lines from the primitive reptiles. Although the physiology of many of the organ systems of birds and mammals are similar, the lungs are radically different. The thesis here is that the bird ended up with a better lung

John West

Although it is customary to emphasize the ways in which the structure and function of the human lung are well-suited to its mission of gas exchange, the opposite case can be made. The proposition here is that the avian lung is superior in many respects to the mammalian lung.

It was about 300 million years ago that the ancestors of the present reptiles emerged from water and made a commitment to air breathing, but they were exothermic and could not sustain high levels of exercise. However, from them came the two great evolutionary lines that produced the mammals and birds, both capable of high, sustained levels of oxygen consumption. A fascinating aspect of these two evolutionary paths is that the physiology of the nervous, cardiovascular, renal, gastro-intestinal, endocrine and skeletal muscle systems show many similarities, but the lungs are radically different. The contention here is that the bird lung is superior to that of the mammal and that evolution got off on the wrong track.

Figure 1 shows the anatomy of the avian and mammalian lungs. Ventilation in the latter is reciprocating with the relatively small tidal volume of each breath being delivered to a relatively large volume of gas already in the lung. In the bird the arrangement is quite different. Inspired air is drawn into air sacs which are avascular and play no part in gas exchange. The gas is then moved through the gas-exchanging parabronchi where the pulmonary capillaries are located, and gas exchange occurs. In other words, this is a flow-through system rather like the radiator of a car, and in fact gas exchange is very similar in many respects to heat exchange. Furthermore, although it is not obvious from Fig. 1, the gas flow through the parabronchi is unidirectional as a result of aerodynamic valving in the airways, although the details of this are still not fully understood.

The reciprocating nature of ventilation in mammals results in at least three potential problems.

1. Potential for uneven ventilation
In resting man, the inspired tidal volume of about 0.5 litres is delivered into a lung volume of about 3 litres. Although the geometry of the airways allows the inspired gas to penetrate far into the lung, the gas cannot reach the peripheral alveoli by convection, and the last part of its movement is by a complicated combination of convection and diffusion in the small airways. As a result, the more proximal alveoli tend to be better ventilated than the more distal, resulting in stratified inequality of ventilation. This inequality is small at rest but increases on exercise when the time available for diffusion is less. The flow-through system in the bird largely avoids this problem.

2. The pool pattern of ventilation reduces the alveolar P_{O_2}
Because a small amount of inspired gas is delivered to a large pool of alveolar gas, the P_{O_2} of the latter is substantially below the inspired value. For example, in the human lung, the inspired P_{O_2} is about 150 mm Hg but the P_{O_2} of the alveolar gas and arterial blood is around 100 mm Hg. Again the flow-through system of the bird largely avoids this problem too.

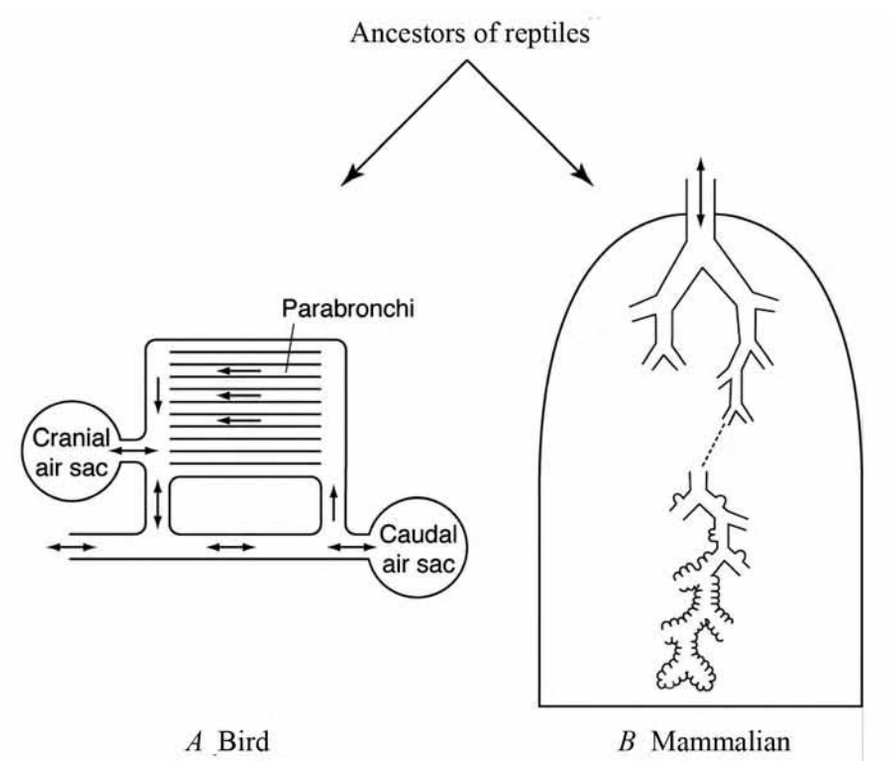

Figure 1 Diagram of the bird and mammalian lungs that both evolved from ancestors of the present reptiles.

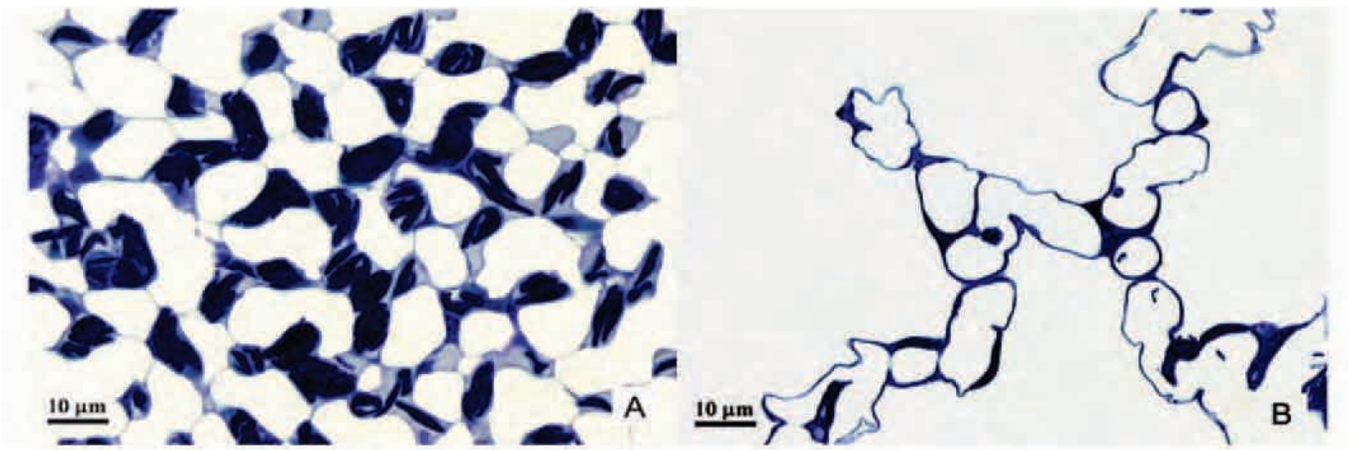

Figure 2 Typical microscopical sections of bird lung (A) and mammalian lungs (B). In the bird the pulmonary capillaries are supported by a dense honeycomb-like network of air capillaries. In the mammalian lung the pulmonary capillaries are spread out along the free-floating alveolar wall.

3. The reciprocating pattern necessitates large terminal air units
Because, as already stated, gas movement to the most peripheral alveoli is by a combination of convection and diffusion, the terminal air spaces need to be relatively large to keep the resistance low. The striking differences between the gas-exchanging tissue of the avian and mammalian lungs are shown in Figure 2. The blood capillaries are similar in size but the air spaces are dramatically different. The bird has air capillaries that branch off the parabronchi or their extensions and their diameter is about 10 to 20 µm depending on the species. By contrast the alveoli of the human lung, for example, have a diameter of about 300 µm.

Some of the disadvantages of these relatively large alveoli have only recently been appreciated. Figure 2B shows that the capillaries are strung out along the alveolar wall rather like a string of beads. This means that they have no mechanical support at right angles to the alveolar wall. As a result the capillary wall has to be thicker. In particular, the extracellular matrix of the blood-gas barrier, which is largely responsible for it strength, needs to be very much thicker than in the bird where the pulmonary capillaries are supported by a network of surrounding air capillaries (West *et al*. 2006). Furthermore, the mammalian alveolar walls require a cable of type 1 collagen that threads its way between the capillaries to maintain the integrity of the relatively large and unsupported alveolar wall. This again thickens part of the blood-gas barrier and thus interferes with diffusive gas exchange.

The mammalian lung has other disadvantages compared with the avian lung but these can only be touched on briefly here. As Fig. 1 indicates, the bird has successfully separated the gas-exchange function of the lung from its ventilatory function. The bioengineering requirements of the tissues for these two functions are very different. Gas exchange by diffusion necessitates an extremely thin blood-gas barrier, for example, it is only 0.2-0.3 µm thick over much of the area of the barrier in the human lung. But the repetitive movement required by ventilation is better done by the more robust air sacs. In fact, one of the commonest, serious lung diseases in humans is emphysema which is characterized by breakdown of the delicate alveolar walls.

Another very practical disadvantage of the mammalian lung is that occlusion of an airway often causes serious impairment of gas exchange. This is a very common problem in the postoperative setting where airways are blocked by retained secretions or aspiration of fluid. Because the same structures are responsible for both ventilation and gas exchange, this is a much more serious problem for mammals than is presumably the case in birds, where aspirated material goes into the nonvascular air sacs.

Another advantage of the avian lung is that the arrangement of air and blood capillaries results in a so-called cross-current pattern of gas exchange, which tends to increase the P_{O_2} of blood leaving the lung. This is well recognized and has been fully discussed elsewhere (Piiper & Scheid, 1972).

Finally, as mammals, we tend to regard ourselves as at the top of the evolutionary heap, but this is arguable. Some birds are superior to any mammals in their mass specific oxygen consumption and their aerobic scope, and there are more species of birds (about 9,000) than mammals (about 4,200).

So why did evolution proceed along an apparently flawed path for mammals. This is probably not a useful question. Evolution does not have a goal but proceeds incrementally. From time to time there is a change in few base pairs which confer an advantage or disadvantage for survival. But the fact that birds have better lungs than ourselves helps to keep a sense of perspective.

Acknowledgements
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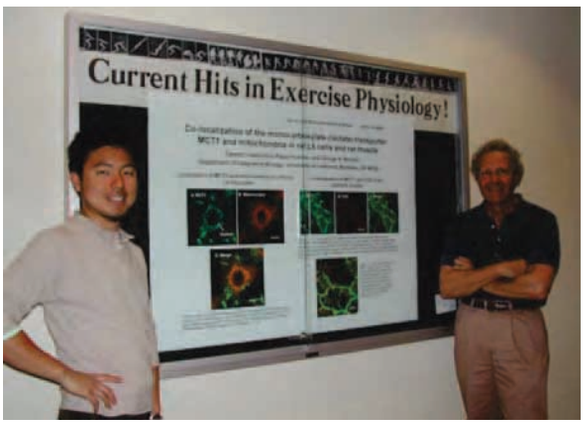
Organization of intermediary metabolism – lactate and its transporters



Takeshi Hashimoto (left) and George Brooks with a poster outside the laboratory

Once thought to be a 'dead-end' metabolite produced because of O_2 insufficiency, lactate is produced continuously under fully aerobic conditions in humans and other mammals. This production serves several functions, key of which is that it is permissive of glycolysis. Lactate is removed mainly by oxidation in red skeletal and cardiac muscle fibres, but also by the liver and kidneys where lactate is the major gluconeogenic precursor. By affecting redox in cells as well as in cell compartments of removal, lactate serves as a signalling molecule. Lactate traverses cell membranes by means of several monocarboxylate (lactate/pyruvate) transport proteins (MCT). Our recent work using microscopy and a variety of techniques shows that MCTs and related proteins occupy cell domains to facilitate the exchange and use of lactate.

Lactate is an end product of glycogenolysis and glycolysis produced only when cells lack oxygen: 'this I learned during my undergraduate studies in Japan', said Takeshi Hashimoto. 'Well, that's what I learned also as an undergraduate in the 1960s', replied George Brooks. 'But', Brooks went on to add, 'as a graduate student and ever since, I could not find proof that lactate is the consequence of O_2-limited metabolism in humans or other mammals.' Rather, the O_2 debt ideas are traceable to early 20th century studies on non-circulated and non-oxygenated amphibian muscle preparations. But now, based on the recent report of Hashimoto *et al.* (2005), as well as related prior investigations, it is time to turn over the classical idea of lactate production due to O_2 lack. Today, we can think of lactate as a substrate for mitochondrial respiration that can be shared among cell compartments, tissues and organs. As well, lactate serves as a gluconeogenic precursor, and as a signalling molecule, a 'lactormone' because of its influence on redox. And, perhaps physiologically more significant is that lessons learned on muscle can be generalized to the functioning of other cells and tissues, including brain (Brooks, 1998).

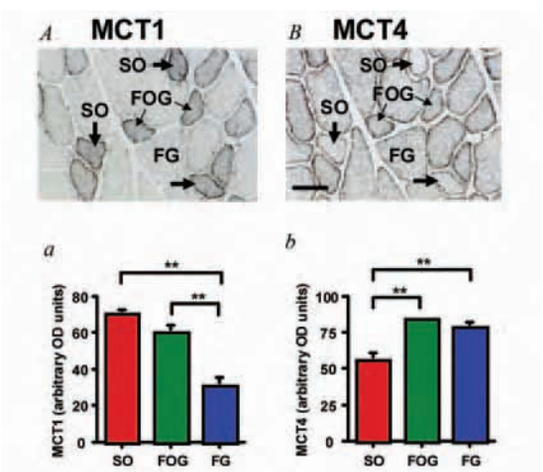


Figure 1. Serial cryostat sections stained for MCT1 (*A*) and MCT4 (*B*). Fibre type identifications were made on the bases of myosin ATPase, SDH, and α-GPD staining (SO, thick arrows; FOG, thin arrows; FG). Very little MCT1 is visible in FG fibres, either at sarcolemmal or interfibrillar cell domains. MCT4 was concentrated at the cell surface in fast (FOG and FG) fibres. Note that in SO fibres MCT1 is strongly stained, while little MCT4 is detected. Scale bar = 50 μm. The quantitative analysis of MCT1 (*a*) and MCT4 (*b*) protein expression in terms of optical density (OD) in different fibre types are shown. Values are expressed means ± SE. **P<0.01.

Based on isotope tracer, arterial-venous difference mass balance and biopsy studies (Brooks *et al.* 1991) we now know that skeletal muscle is not only the major site of lactate production, but also the major site of its removal, mainly via oxidation. Lactate and pyruvate are exchanged across muscle cell (sarcolemmal) membranes by facilitated, proton-linked transport (Roth & Brooks, 1990) involving a family of MCT proteins (Garcia *et al.* 1994). MCT1 is widely expressed in different tissues and has been localized in muscle to sarcolemmal and mitochondrial membranes (Brooks *et al.* 1999; Hashimoto *et al.* 2005), and facilitates uptake of lactate from interstitium and plasma. The putative role of MCT4 is cellular lactate extrusion. Up to now, Brooks and associates have posited two major lactate shuttles:

• the cell-to-cell lactate shuttle: lactate formed in some muscle cells with high rates of glycolysis can shuttle to other cells with high oxidative capacity via sarcolemmal lactate transporters and be oxidized (Brooks, 1998)

• the intracellular lactate shuttle (ILS): lactate enters mitochondria and is oxidized to pyruvate via mitochondrial lactate dehydrogenase (LDH) when mitochondrial redox decreases, and

pyruvate is oxidized via the tricarboxylic acid cycle and electron transport chain (Brooks *et al*. 1999).

However, the existence of mitochondrial MCT1 and LDH has been controversial. Until our recent paper (Hashimoto *et al*. 2005), no one had quantified MCT isoform expression by histochemical assessment. Consequently, it was unclear whether MCTs occupied the same or different cell domains in different muscle fibre types. To better understand the physiological roles of MCTs and related proteins, such as mitochondrial inner membrane protein cytochrome oxidase (COX), we sought to determine the distribution and relative abundances of MCTs in rat plantaris that contains different muscle fibre types. Quantitative immunohistochemical determination of MCTs by the high sensitivity avidin-biotin complex (ABC) method showed that MCT1 is located at the sarcolemma and throughout the cell interior in oxidative fibres; in contrast, MCT4 is highly expressed in the sarcolemmal domain of glycolytic fibres (Fig. 1). As well, confocal laser-scanning microscopy (CLSM) demonstrated that MCT1 and COX are co-localized at both interfibrillar and subsarcolemmal cell domains (Fig. 2A). These results show that MCTs and associated proteins are positioned to facilitate function of the lactate shuttles: lactate formed in some muscle cells with high rates of glycolysis (e.g. fast-glycolytic, FG fibres) could be readily released via MCT4 (and MCT1) and transported into slow and fast oxidative (SO and FOG) fibres via sarcolemmal MCT1 lactate transporters. In conjunction, mitochondrial MCT1 facilitates lactate uptake, as oxidation is the major means of intramuscular lactate disposal and therefore essential in establishing the concentration and pH gradients that drive cellular lactate release, uptake and disposal.

As to the controversy surrounding mitochondrial MCT1 and LDH, we provide strong evidence of their existence. The single-span transmembrane glycoprotein CD147 (BSG, or Basigin) is considered to be the chaperone protein for MCT1

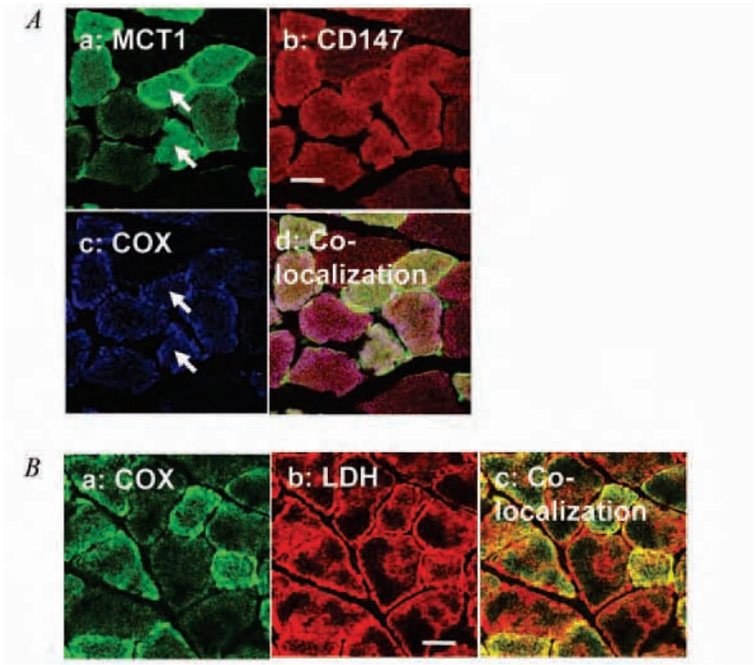


Figure 2. Cellular locations of *A*, MCT1, CD147 and COX, and *B*, COX and LDH determined using confocal laser scanning microscopy (CLSM) and fluorescent probes for the respective proteins. In *A*, MCT1 was detected throughout the cells including subsarcolemmal and interfibrillar domains of oxidative fibres (arrows: plate a and c). CD147, anchoring protein of MCT1 (plate b) is localized corresponding to MCT1 (plate a). When these MCT1 (green), CD147 (red), and COX (blue) were merged, superposition of the two probes was clear (white: plate d). In *B*, when these COX (green) and LDH (red) were merged, superposition of the two probes was clear (yellow: plate c). Scale bar = 20 μm.

localizing it to the cell surface. Like MCT1 (Fig. 2A-a), we detected CD147 throughout rat plantaris muscle fibres (Fig. 2A-b). Furthermore, MCT1 (Fig. 2A-a), CD147 (Fig. 2A-b), and COX (Fig. 2A-c) were co-localized in individual fibres of rat plantaris muscle (Fig. 2A-d). These findings indicate the existence of MCT1 at mitochondrial inner membrane associated with CD147. Furthermore, we showed the co-localization of COX (Fig. 2B-a) and LDH (Fig. 2B-b) as a yellow colour in Fig. 2B-c, indicating the existence of LDH in mitochondria. Additionally, in cultured L6 skeletal muscle cells, we also observed associations among mitochondrial MCT1, CD147, COX and LDH by both CLSM and immunoprecipitation technique (Hashimoto *et al*. 2006). Although not yet definitive, results are consistent with presence of a sixth, lactate oxidation, mitochondrial complex.

So, what is the pace of progress? Takeshi Hashimoto learned classic 'O_2 debt' theory in the late 1990s. Now, checking PubMed there are hundreds of hits for 'MCT1' and the 'lactate shuttle', where much recent activity has been in the realm of neurobiology.

Brooks' sons Dan and Tim (now 29 and 27 years old) grew up with O_2 debt theory in the biology curriculum. But, will Kengo Hashimoto (18 months old) have the same experience?

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Endothelial nitric oxide synthase-derived NO signals regulate microvascular permeability

Regulation of vascular tone is largely dependent on the production of nitric oxide (NO) by the endothelium. Recent findings provide compelling evidence supporting an important role for endothelial NO in the regulation of microvascular permeability

Walter Durán (above, left), Takuya Hatakeyama (above, right) and Fabiola Sánchez (left)

Inflammation is recognized as a fundamental underlying alteration in many diseases. One of the hallmarks of inflammatory processes is an increase in microvascular permeability (hyperpermeability) to macromolecules. An important function of hyperpermeability is to allow the movement of macromolecules for tissue healing and remodelling in response to injurious stimuli. Under inflammatory conditions, microvascular permeability to macromolecules is controlled mainly at the postcapillary venules. The coordination of appropriate physiologic responses to the changing tissue environment *in vivo* is coordinated through signalling interactions between blood cells, vascular wall and parenchymal cells.

Nitric oxide is recognized as an important signalling regulator of cardiovascular function, but its role in the control of microvascular permeability was regarded as controversial. Evidence in tissues and in isolated venules demonstrated that the activity of endothelial NO synthase (eNOS) increases microvascular permeability to macromolecules in response to inflammatory agents (Ramírez *et al*. 1995; Yuan *et al*. 1993). Other results indicated that NOS activity prevents increases in permeability (Kurose *et al*. 1995). In either view, the evidence for endogenous NO involvement as a positive or negative modulator of permeability was persuasive but not necessarily compelling as it was based mainly on the ability of L-arginine analogs to block NOS non-specifically.

The development of genetically engineered mice has contributed importantly to evaluate more directly the function of eNOS in microvascular permeability, with the appropriate caveats related to the adaptive changes occurring in response to deletion of important genes. Using eNOS-/- mice, we and others demonstrated that deletion of the gene encoding for eNOS prevents mounting an appropriate hyperpermeability response to VEGF (vascular endothelial growth factor) in skin (Fukumura *et al*. 2001) and to PAF (platelet-activating factor) in cremaster muscle and in mesentery (Hatakeyama *et al*. 2006). Figure 1 illustrates the dramatic difference in the PAF-induced hyperpermeability response in mouse cremaster. Changes in microvascular permeability were evaluated in the interstitial space by integrated optical intensity (IOI) using fluorescently labelled dextran (FITC-dextran 70, with mean molecular weight = 70,000 daltons) as a macromolecular indicator. Topical application of PAF caused an increment from a baseline value of 2.4 ± 2.2 to a peak net value of 84.4 ± 2.7 units in wild-type mice; whereas in mice lacking the eNOS gene (eNOS-/- mice) PAF increased IOI only from a baseline of 1.0 ± 0.3 to a peak net value of 15.6 ± 7.7 units. Figure 1 also demonstrates the extravasation of FITC-dextran 70 through a series of images captured by intravital microscopy and computer-assisted digital image analysis.

Importantly, we demonstrated that eNOS was the relevant nitric oxide synthase in this NO-regulated response as we established that mice lacking the gene encoding for inducible NOS (iNOS) produced a hyperpermeability to PAF that was of comparable magnitude to that of wild-type mice

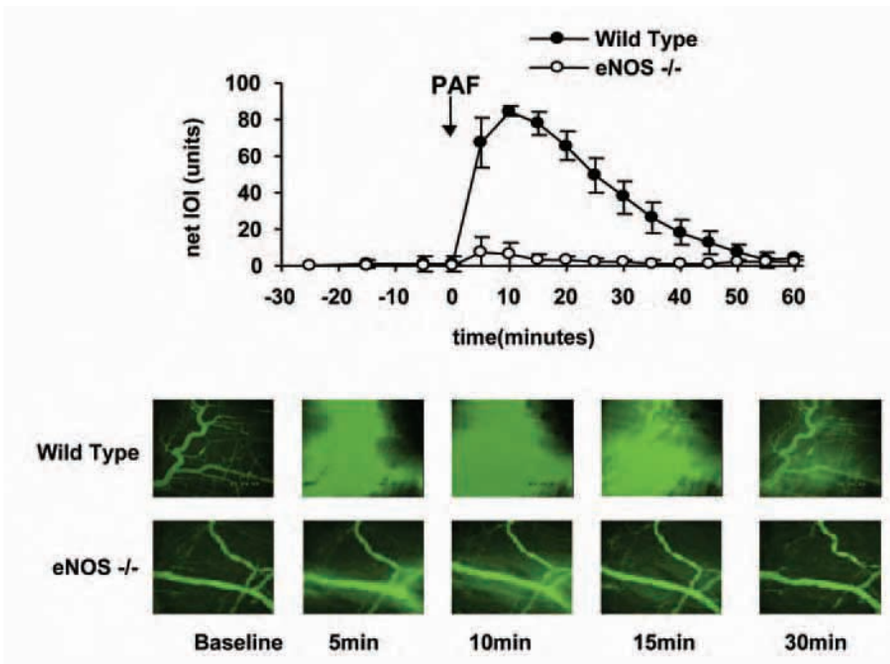

Figure 1. Deletion of the gene encoding for eNOS (eNOS-/-) prevents PAF-induced hyperpermeability in mouse cremaster muscle. ***Top panel*** shows changes in microvascular permeability using integrated optical intensity (IOI), expressed in arbitrary units, as an index. ***Bottom panel*** shows images of PAF induced changes in permeability in cremaster muscles of wild-type and eNOS -/- mice (modified from *J Physiol* **574**, 275-281, with permission).

(Hatakeyama *et al*. 2006). We also showed that inhibition of eNOS by caveolin-1 scaffolding domain (an endogenous cellular regulator of eNOS activity) reduced the ability of PAF to increase microvascular permeability in cremaster muscle and mesentery of wild-type mice (Hatakeyama *et al*. 2006). The clinical significance of eNOS-derived NO is manifested by the reduction in postischemic microvascular permeability observed in cremaster muscle of eNOS-/- mice relative to wild-type mice (unpublished data) and by the increase in pulmonary microvascular permeability in caveolin-1 deficient mice (Schubert *et al*. 2002). Several laboratories, in further support of regulation of microvascular permeability by eNOS-derived NO, have documented that inhibition of eNOS decreases transport of macromolecules across monolayers of endothelial cells, whereas substances that phosphorylate eNOS and enhance NO production increase it (Lal *et al*. 2001; Yuan, 2000).

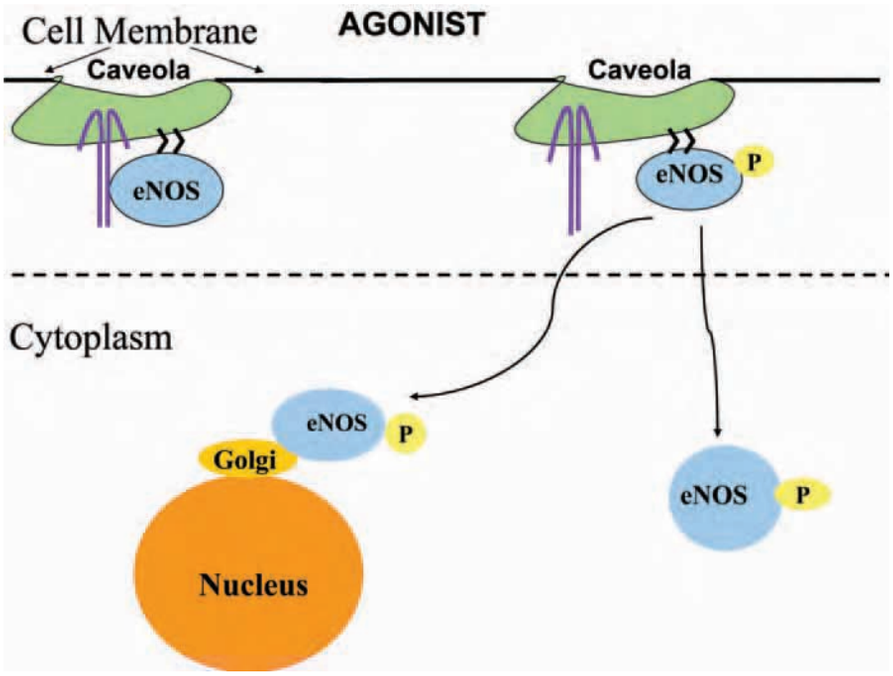

Figure 2. Simplified diagram of eNOS translocation hypothesis. eNOS is shown anchored (through myristoylation and palmitoylation) in caveolae and associated with caveolin-1 (purple arrows) in baseline conditions in endothelial cells. Upon stimulation by agonists, eNOS becomes phosphorylated, it dissociates from caveolin-1 and translocates from the caveolae to either Golgi or cytosol. It is postulated that translocation to the Golgi or cytosol compartments is related to vascular function and may allow eNOS to interact with its specific function-related target proteins.

Mechanisms of signal transduction in hyperpermeability

Much remains to be learned about how eNOS-derived NO signals for permeability regulation in microvascular endothelia. While the gene sequence of eNOS is highly conserved among species, the post-translational regulatory modalities may vary in different species. A potentially important regulatory mechanism reported early is the phosphorylation of eNOS by Akt (Fulton *et al*. 1999). However, recent data raise questions as to the specificity conferred to the signal by Akt-induced phosphorylation, particularly at Serine-1179. The questions are based on the observation that, while necessary, this phosphorylation step is common to several different NO-associated vascular functions – such as permeability, vasodilation, angiogenesis, and cell survival (Sánchez *et al*. 2006). The question is fundamentally valid even though several eNOS phosphorylation sites have been described along with regulation of the enzyme by protein-protein interactions, some of which may represent novel mechanisms or pathways (Dudzinski *et al*. 2006).

Enzyme location is of importance to achieve its specific function. Endothelial nitric oxide synthase is found mainly in the cell membrane, but it is also well represented in Golgi under baseline conditions. The relationship between eNOS location and function might be of utmost relevance in endothelium due to the high NO-scavenging capacity of blood haemoglobin. Translocation of eNOS from membrane to other cell compartments in response to agonists has been documented by several techniques including conventional and confocal fluorescence microscopy as well as western blotting. Cellular location of eNOS may represent a mechanism that determines the rate of NO production under different physiological or experimental conditions. Whether translocation represents a defined mechanism or a step in signalling to bring the enzyme closer to its functional target remains to be determined. The diagram in Fig. 2 describes a simplified view of experimental evidence indicating that differential translocation of eNOS is associated to microvascular function. Using agonists that afford a relatively clear discrimination between precapillary and postcapillary functions (basically vasodilation versus permeability), we observed in cells in culture that acetylcholine (a 'pure' vasodilator) induces preferential translocation to Golgi, whereas PAF (a hyperpermeability inducing agent) caused translocation preferentially to the cytosol (Sánchez *et al*. 2006). The basis for the physiological translocation of eNOS *in vivo* has been demonstrated elegantly in transgenic mice using a fluorescent label that allows tracking the enzyme location *in vivo* (Cheng *et al*. 2005).

The biological or experimental basis for the earlier controversy regarding NO regulation remains unknown, but it may reside in species differences and in inherent limitations of the use of non-specific pharmacologic agents. Compelling evidence based on the use of genetically engineered mice demonstrates that eNOS-derived NO regulates the necessary hyperpermeability in postischemic

tissues and in inflammation. Despite abundant and sophisticated information obtained in cell cultures, the door is wide open for studies to elucidate the mechanisms by which eNOS-derived NO exactly and specifically regulates microvascular permeability *in vivo*.

Acknowledgments

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Acute pain

Pain is a perceptual experience that is ascribed to a body part and has a negative effect. Under normal circumstances, the stimuli that elicit pain are tissue-damaging or would cause tissue damage were they to persist: in short, noxious stimuli. Under these same conditions, noxious stimuli elicit a report of pain in verbal humans.

While the gold standard for pain perception will always be verbal report, ontological and phylogenetic continuity are most consistent with the idea that non-verbal humans and animals, at least mammals, experience pain. I will therefore use the terms pain and painful stimulus to refer to what others term nociception and noxious stimulus. A fundamental distinction can be drawn between acute pain – a transient experience – and persistent or chronic pain. Acute pain requires a stimulus to engage nociceptive pathways. In many forms of chronic pain, no stimulus occurs and nociceptive pathways are activated pathologically.

Acute pain is a common experience of varied intensity, location and meaning. Stubbing a toe or being scratched by a loving pet is transiently bothersome but rapidly forgotten. In contrast, breaking a toe or scratching a cornea evokes intense pain and the circumstances surrounding such events are long remembered. The acute pain experience is at turns protective and debilitating. Short-latency motor reactions to superficial pain stimuli, commonly withdrawals, are protective as are the longer latency, affectively motivated escape strategies including flight and freezing. Although freezing may not commonly be thought of as an escape reaction, it is preferred to flight when a rodent faces a predator within close quarters and serves the same function as flight does in more spacious conditions.

Pain can also be arresting, as anyone that has experienced an acute episode of back pain knows. Immobility (an active state with high muscle tone)

Peggy Mason

elicited by extreme pain is clearly to an individual's disadvantage, rendering her or him vulnerable to predators or potentially injurious situations. One may postulate that while failing to serve an individual's immediate safety needs, painful stimulus-evoked immobility is necessary to allow healing from an injury. According to this idea, if one moved about with a ruptured disk, the disk would never heal, a reasonable possibility supported by the prevalence of prescribed bed rest for myriad painful conditions. Thus being frozen in pain may be the only long-term solution to injury despite its immediate inconveniences. Finally, it should be noted that prolonged immobility is survivable only by humans and other highly social animals and is likely lethal in less social species.

In addition to evoking either movement or active immobility, painful stimulation can also be ignored. This happens when animals are feeding, voiding, or highly stressed (Baez *et al*. 2005; Foo & Mason, 2005). For example, a rat that is eating chow will continue eating chow as heat is applied to his hindpaw, typically never responding to the heat stimulus that causes a brisk withdrawal when the rat is not eating. While one may assume that extremely intense noxious stimuli would elicit a reaction under all circumstances, ethical concerns preclude these experiments and therefore only mild to moderate intensity stimuli are used. Allowing for context-specific modulation of noxious input allows for behavioral flexibility.

Furthermore, this flexibility can serve to adjudicate between the needs of an

organism. For example, a rat that has had difficulty finding food may continue to eat, notwithstanding intense noxious stimulation. In contrast that same intense noxious stimulation will likely interrupt a rat that has recently fed. Under natural circumstances, food is relatively scarce and the system may be biased toward feeding, resulting in the failure of moderately painful stimuli to interrupt feeding.

Within the category of acute pain, there are significant differences and few similarities between cutaneous and deep pain. A noxious cutaneous stimulus typically leads to active movements away from the offending situation accompanied by multiple signs of sympatho-excitation. The resulting pain perception is well demarcated in time and space and if of sufficient intensity, a long term memory of the event will ensue. In contrast, a noxious deep stimulus does not elicit movement and often is not immediately accompanied by perception, thereby precluding explicit memory formation of the surrounding circumstances. When of sufficient intensity, deep injury can lead to perception, albeit poorly localized in time and space, as well as immobility and sympatho-inhibition.

Several glaring examples of the subtle effects of deep injury have recently been reported. In one such example, a nail gun backfired, sending a nail into the cheek of the young man operating the gun. After receiving treatment for the cutaneous wound in his cheek, the man returned home. Only a week later, after presenting with a toothache, did it become clear that the nail had actually entered the young man's cranium and was lodged therein (see Fig. 1). Perhaps even more remarkable was the fact that this was the second such case observed at the suburban Denver hospital where the injury was treated. It is telling to contrast the immediate indifference evoked by such a severe deep tissue injury as described above with the inordinate concern and awareness that accompanies a superficial injury such as a paper cut.

In sum, it is clear that cutaneous and deep pain are very different

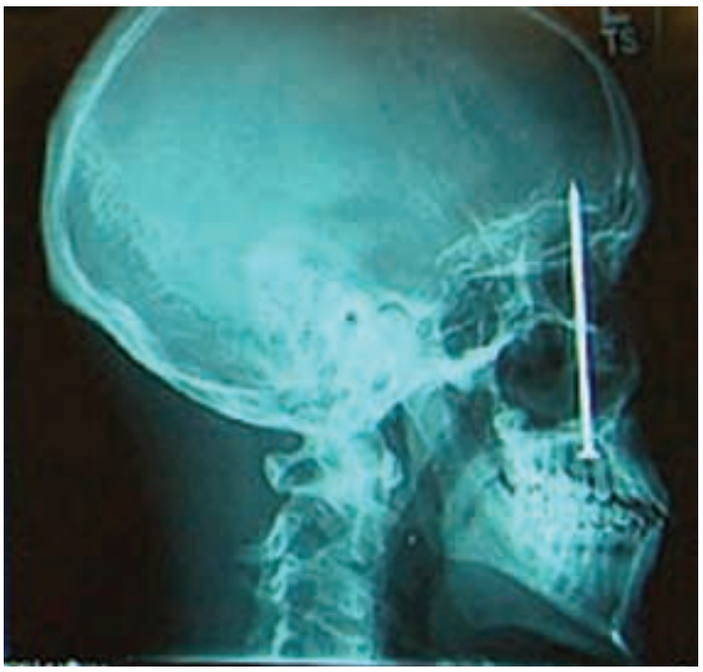

Figure 1. A glaring example of the subtle effects of deep injury. A nail gun backfired, sending a nail into the cheek of the young man operating the gun. Only a week later, after presenting with a toothache, did it become clear that the nail had actually entered the young man's cranium and was lodged therein (*photograph courtesy of the Littleton Adventist Hospital, Colorado, USA*).

phenomenologically, leading Thomas Lewis, an early pioneer in pain research, to lament that the somatic experiences of deep and superficial pain share a common moniker (Lewis, 1942).

Several differences exist between the neural mechanisms that support acute cutaneous and deep pain.

Afferents carrying information about cutaneous pain belong to a specific class of nociceptors that are activated only by noxious stimuli that would normally elicit pain. Afferents that carry deep pain input are more heterogeneous with some coding pain exclusively, like cutaneous nociceptors, and some that code both pain and non-painful information.

Another difference between cutaneous and deep pain is the role of descending modulation from the brainstem and forebrain. The net effect of descending modulation onto cutaneous nociceptive pathways is a tonic inhibition. In marked contrast, it appears that for visceral nociception, a spino-bulbo-spinal loop is **required** for expression of the full behavioral and physiological reaction (Cervero *et al*. 1985; Ness & Gebhart, 1988).

Taking the differences in behaviour and neural circuitry together leads to the Gertrude Stein-esque conclusion that 'acute pain is not acute pain is not acute pain'. Put more positively, acute pain is heterogeneous, depending on location, intensity, and context.

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Legs pay out for cost of breathing!

Lee Romer and Jerome Dempsey propose that the demand placed on the respiratory muscles during high-intensity endurance exercise plays a pivotal role in determining exercise performance through its effect on limb blood flow and muscle fatigue

The respiratory muscles are, with few exceptions, structurally suited to the high ventilatory demands of endurance exercise. The diaphragm, for example, has a high oxidative capacity, multiple sources of blood supply and a unique resistance to vasoconstrictor influences, making it the most fatigue resistant of all skeletal muscles. Such structural characteristics, in combination with precise neural regulation of breathing pattern and respiratory muscle recruitment, mean that the capacity of these muscles for pressure generation is usually well in excess of the demands placed upon them. Thus, in most untrained healthy individuals the pressures produced by the inspiratory muscles during progressively increasing exercise are only about 50% of maximum dynamic capacity, the oxygen cost of breathing approximates 10% of maximum oxygen uptake and diaphragm fatigue does not occur.

Despite the considerable aerobic capacity of the diaphragm, this muscle will fatigue in response to exercise sustained to exhaustion at intensities greater than 80-85% of maximum oxygen uptake. For example, the pressure measured across the diaphragm in response to bilateral stimulation of the phrenic nerves (1-20 Hz) was reduced 15-50% below pre-exercise baseline and did not return to control values until 1-2 hours after exercise (Johnson *et al.* 1993). The reason for this exercise-induced diaphragmatic fatigue is due in part to the high levels of diaphragmatic work that must be sustained throughout high-intensity exercise, as demonstrated by the finding that diaphragmatic fatigue was prevented when diaphragmatic work during exercise was reduced by over 50% using a mechanical ventilator. However, other factors besides diaphragmatic work must also be responsible for the exercise-induced diaphragmatic fatigue, because fatigue does not occur when the resting subject mimics the magnitude and duration of diaphragmatic work incurred during exercise. Indeed, fatigue does not occur until diaphragmatic work is voluntarily increased two-fold greater than that required during maximal exercise. The probable explanation of this substantial effect of whole body exercise on diaphragm fatigability is that, at rest, the volitional increases in diaphragmatic work mean large shares of the total cardiac output are devoted to the diaphragm, whereas during exercise the diaphragm must compete with locomotor muscles for their share of the available cardiac output. Less blood flow to the diaphragm promotes inadequate oxygen transport and increases the likelihood of fatigue.

Jerome Dempsey (left) and Lee Romer

The aforementioned physiological effects of the work of breathing have important functional consequences, as demonstrated by an approximately 15% improvement in performance during high-intensity endurance exercise with partial unloading of the respiratory muscles via mechanical ventilation (Harms *et al.* 2000). One aspect of respiratory muscle work that might limit exercise performance is a reflex effect from fatiguing respiratory muscles, which increases sympathetic vasoconstrictor outflow and compromises perfusion of limb muscle thereby limiting its ability to perform work. Fatiguing contractions and accumulation of metabolites in the respiratory muscles activate the unmyelenated Type IV phrenic afferents

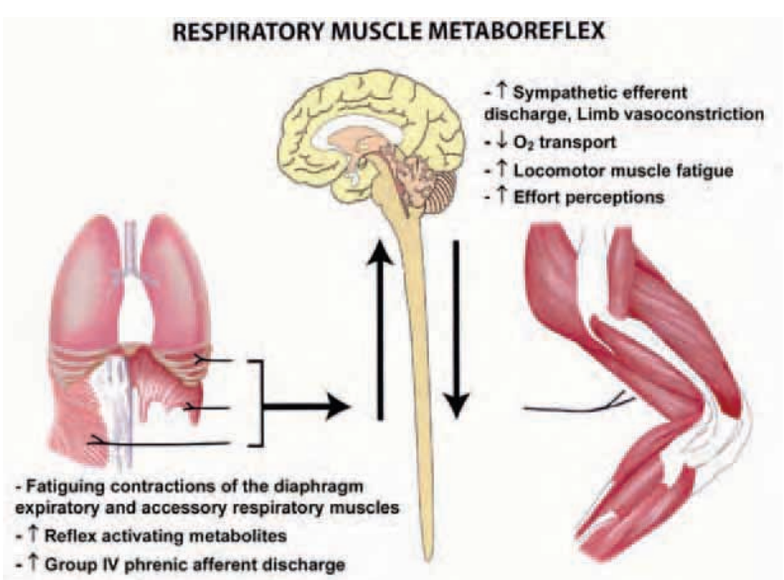

Figure 1. Schematic of the proposed respiratory muscle metaboreflex and its effects. The metaboreflex is initiated by fatigue of the inspiratory muscles, mediated supra-spinally via phrenic afferents, leading to sympathetically mediated vasoconstriction of limb locomotor muscle vasculatures, exacerbating peripheral fatigue of working limb muscles and (via feedback) intensifying effort perceptions, thereby contributing to limitation of high-intensity, endurance exercise performance.

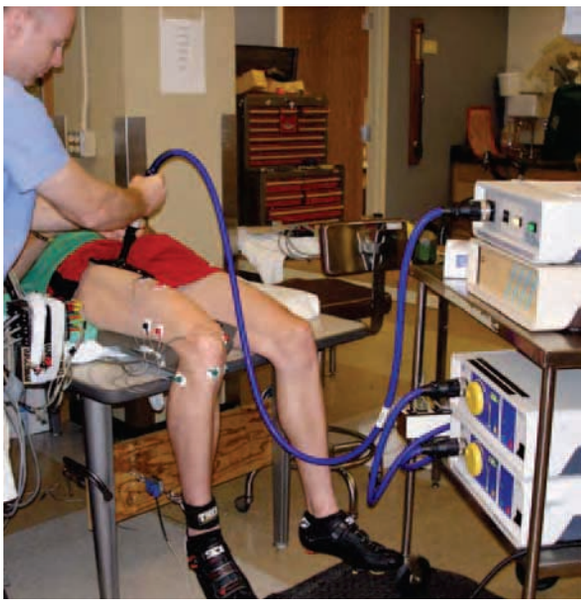

Figure 2. Stimulation of the femoral nerve using a double coil connected to two magnetic stimulators. Quadriceps muscle force output was assessed using a force transducer connected to a strap around the subject's right ankle. The potentials (M-waves) evoked from the quadriceps via nerve stimulation were measured using surface electromyography.

which, via a supraspinal reflex, evokes an increase in muscle sympathetic nerve activity (St Croix *et al.* 2000) and a reduction in blood flow and vascular conductance in the resting leg (Sheel *et al.* 2001) (see Fig. 1). During maximal exercise, concomitant increases in vascular conductance and blood flow to working limb muscles have been observed when the normally occurring work of breathing is reduced using a mechanical ventilator (Harms *et al.* 1997). Furthermore, in resting and exercising dogs, a bolus injection of lactic acid into the diaphragm by way of the phrenic artery elicits a transient reduction in hind limb blood flow and vascular conductance – these changes appear to be mediated sympathetically because they are prevented by pharmacological blockade of the adrenergic receptors (Rodman *et al.* 2003).

In our most recent experiments we attempted to determine whether the aforementioned changes in vascular conductance and limb blood flow with manipulation of the work of breathing impact upon the fatigability of the working limb muscles (Romer *et al.* 2006). We assessed limb muscle fatigue by magnetically stimulating the femoral nerve using a paired twitch technique (see Fig. 2). Force:frequency curves for the quadriceps were constructed by altering the duration between paired twitches. These measurements were performed before and after high-intensity cycle exercise under conditions of control, inspiratory muscle unloading (via mechanical ventilation) and inspiratory muscle loading (via inspiratory resistors). When exercise at 90% of peak work rate was continued to exhaustion with breathing unimpeded, quadriceps twitch force averaged across a wide range of stimulation frequencies (1-100 Hz) was reduced by almost 30% in the period immediately after exercise. When the exercise was repeated on a different day at equal workload and duration as the control condition, but with the normally occurring work of breathing reduced by 50-60%, the decrease in quadriceps force output was attenuated by about one-third. Increasing the work of breathing by 80% above control exacerbated the severity of fatigue by about 40% compared with identical exercise with breathing unimpeded.

The effect of inspiratory muscle unloading on limb muscle fatigue was consistent among subjects but relatively small compared with the much larger reductions in limb fatigue we recently found by preventing the mild arterial oxygen desaturation that can accompany high-intensity exercise. Nevertheless, it is likely that this effect of unloading on fatigue represents an underestimation of what might be attributed to the total work of breathing. For example, the normal work of breathing was reduced by only slightly more than one half. Furthermore, the loading and unloading arms of the study were confined to inspiration. Recent evidence in healthy individuals suggests that the expiratory abdominal muscles also fatigue in response to high-intensity endurance exercise and that expiratory loading to the point of task failure elicits an increase in leg muscle sympathetic nerve activity. Furthermore, the high expiratory pressures often encountered during high-intensity exercise in response to active expiration and expiratory flow limitation have been shown to reduce stroke volume, which may be expected to exacerbate limb fatigue via concomitant reductions in limb blood flow.

In health, it is likely that exercise-induced respiratory muscle work contributes to limb fatigue only during sustained high-intensity exercise that is sufficient to elicit significant levels of fatigue in the diaphragm or accessory respiratory muscles. Environmental hypoxia, and particularly chronic hypoxic exposure which potentiates the hyperventilatory response to exercise and consequently the work of breathing, might also be expected to exacerbate the effect of respiratory muscle work on limb fatigue. From a clinical perspective, changes in the work of breathing may play a particularly important role in determining limb fatigue in patients with chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF). In patients with COPD the limb muscles are more fatigable than in healthy subjects and the inspiratory and expiratory pressures developed during exercise are substantial. Many such patients exhibit a plateau in leg blood flow early during progressively increasing exercise and these patients also tend to have the highest levels of ventilation and dyspnea during exercise, suggesting that blood flow may be redirected to the respiratory muscles. Patients with CHF also have an elevated work of

breathing, in addition to blunted cardiac output and sympathetic vasoconstrictor responses to exercise. In combination, these factors could compromise limb blood flow and fatigue, even during submaximal exercise.

In summary, unloading the respiratory muscles in normal healthy individuals improves performance during high-intensity exercise coincident with increases in limb vascular conductance and blood flow and a reduction in leg muscle fatigue. We propose that exercise-induced respiratory muscle work contributes to both 'peripheral' and 'central' fatigue influences on exercise performance. In other words, quadriceps muscle fatigue plays a pivotal role in determining exercise performance both through its direct effect on muscle force output (i.e., peripheral fatigue) and also through its feedback effect on effort perceptions, causing reduced motor output to the working limb muscles (i.e., central fatigue).

Acknowledgements
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Functional domains of tropomyosin: new insights

Functional studies of tropomyosin molecule using transgenic approaches reveal that its inner core region has a greater effect on calcium sensitivity of the myofilaments and the carboxy terminal ends regulate the TM-actin affinity and/or crossbridge kinetics

Tropomyosin (TM) is a thin filament regulatory protein that is intricately involved in cardiac muscle contraction. Working in conjunction with the troponin complex, TM's position on actin either blocks or exposes myosin-binding sites, and thus prevents or allows crossbridge formation as outlined in the three state model of muscle contraction (McKillop & Geeves, 1993).

Mariappan Muthuchamy (left) and Robert Gaffin

The principal focus of our lab has been to address the role of TM in cardiac muscle function. Initial findings using β-TM transgenic (TG) mouse model demonstrated that β-TM TG hearts displayed diastolic dysfunction including increased time to one-half relaxation and a decreased maximum rate of relaxation in working heart preparations, increased calcium sensitivity in skinned fibres.

Two important charge modifications in β-TM, Ser229Glu and His276Asn, give it a charge that is more negative than α-TM. Since the remaining residue differences between the two isoforms involve rather conservative polar or non-polar changes, we hypothesized that generating β-TM's two charge modifications on an α-TM background would produce results identical to those seen in β-TM TG mice. Thus, we generated 'double mutation' (Ser229Glu and His276Gln) TG mouse lines. These TG mice exhibited decreased Ca^{2+}-sensitivity in skinned fibres as well as a decrease in both the rate of contraction and relaxation in working heart preparations (Gaffin *et al*. 2004a).

We then wished to see the effects of these two charge changes on an individual basis. α-TMSer229Glu TG mice exhibited a decrease in myofilament calcium sensitivity and a decrease in both +dP/dt and -dP/dt in the working heart while α-TMHis276Asn TG mice did not alter calcium sensitivity but decreased -dP/dt (Gaffin *et al*. 2004b). Furthermore, TG mouse lines that express a mutant form of α-TM in which the first 275 residues are from α-TM and the last nine amino acids are from β-TM (α-TM9aaΔβ) exhibit decreased rates of contraction and relaxation in working heart studies (Gaffin *et al*. 2006). The myofilaments containing α-TM9aaΔβ protein demonstrate a normal pCa-force relationship (Gaffin & Muthuchamy, unpublished data). These data indicate that the function of TM is compartmentalized along its length (Fig. 1).

We propose that residues located near the site where TM interacts with the C-terminus of TnT (which also interacts with the C-terminus of troponin C (TnC), the myofilament's calcium sensor) primarily affect calcium sensitivity since α-TMSer229Glu caused a decrease while α-TMHis276Asn and α-TM9aaΔβ had no effect. On the other hand, α-TMHis276Asn and α-TM9aaΔβ mutations located in the carboxy terminus of TM, have altered the rates of contractile dynamics without affecting calcium sensitivity.

To explain this, we point to the fact that the carboxy terminus affects TM-actin affinity in the 'open' state of muscle contraction as proposed by Hitchcock-Degregori's group (Moraczewska *et al*.

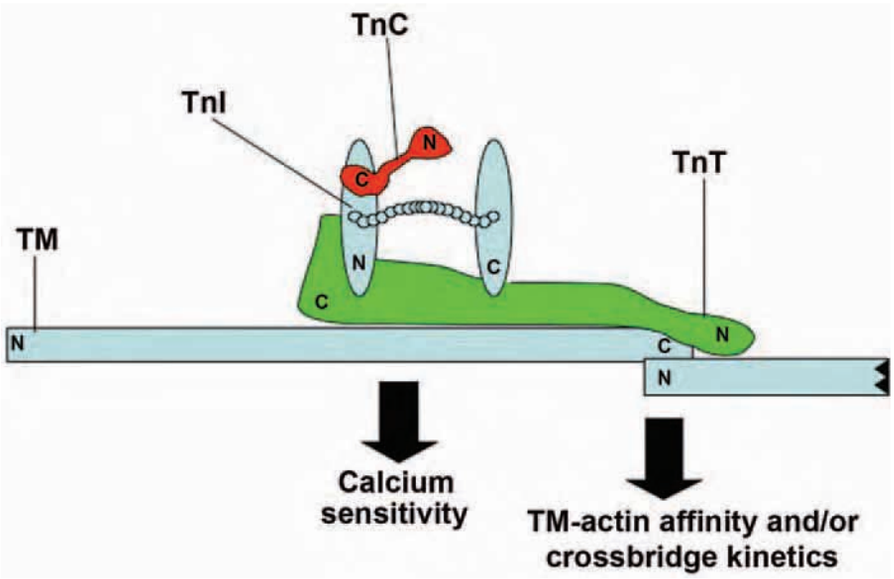

Figure 1. Compartmentalisation of TM's function along its length. Schematic representation of tropomyosin (TM) and troponin complex interaction is shown. In the inner core region of tropomyosin (TM), the C-terminus of troponin T (TnT) binds to TM as well as to the C-terminus of both TnC and the N-terminus of troponin I (TnI). At the overlap region of TM, the N-terminus of TnT interacts. Residues near the inner core region of TM primarily affect calcium sensitivity due to the proximity of the myofilament's calcium sensor, TnC. Residues in the C-terminus of TM primarily affect TM-actin affinity and/or crossbridge kinetics.

1999). An enhancement of TM-actin affinity during this phase would delay the myofilament's transition from the 'open' to the 'blocked' state thus affect contraction and relaxation kinetics in α-TM His276Asn and α-TM9aaΔβ TG mice.

Compartmentalization of TM function is further evidenced by the recent work of Dr Wieczorek's group. TG mice expressing chimeric TM protein (exons 1–8 [residues 1– 257] from α-TM plus exon 9 [residues 258–284] from β-TM) exhibit decreased rates of contraction and relaxation in whole heart studies, and a decrease in calcium sensitivity in skinned fibres (Jagatheesan *et al*. 2003). In addition, exchanging the TnT binding domains of α-TM amino acids [175–190 and 258–284] with the β-TM regions decreases the rates of contractile dynamics; however, the calcium sensitivity is not altered (Jagatheesan *et al*. 2004).

These results, along with our data, point out the complexity of the relations between structure and function of TM molecule. Each difference exists between the α- and β-TM molecules such as TnT binding domains, charge residue changes or the changes in the carboxy terminal ends contribute to the contractile dynamic changes and/or calcium sensitization of the myofilaments. However, none of these changes, either individually or in combination within the α-TM molecule, mimic the function that is seen in the β-TM TG mice. In addition, these TG mice functional studies reveal there is a lack of correlation between the force-calcium relationships and the haemodynamic measurements at the myofilaments and the whole heart levels, respectively, indicating a cautious extrapolation/ correlation of the physiological and biochemical parameters of cardiac function. On the other hand, both calcium activation of the thin filament and positive feedback by strong crossbridges mechanisms make significant contributions to each phase of the contractile cycle. Further analytical tools to quantify the contributions of the calcium or crossbridge cooperative effects to each phase of the contractile cycle would be useful to address the mechanisms of TM function in the myofilament activation processes.

In summary, we conclude that the function of α-TM is compartmentalised along its length. Sequences nearer the inner core of TM have a greater effect on calcium sensitivity due to their proximity to the TnT-TnC interface while residues in the carboxy terminus affect either TM-actin affinity or crossbridge kinetics. Furthermore, these studies support the idea that the localised flexibility present in the coiled coil structure of various TM isoforms are different, and that plays an important role in interacting with neighboring thin filament regulatory proteins and differentially modulating the myofilament activation processes.

Acknowledgements

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The study of nociception from periphery to brainstem

An International Workshop at the Bogomoletz Institute for Physiology, Kiev, Ukraine, 4-7 June 2006

Taking an idea through to fruition: organizing an International Workshop in Kiev

For the organizers of any international event, one of the fun parts is sitting casually over a glass of wine and drafting a list of high profile participants to invite to your event. It is not always the case that the 'wish list' becomes reality but this certainly was the case for our Kiev-based student workshop. Perhaps it was the fact that it was to be hosted in the eponymous Bogomoletz Institute of Physiology which, under the leadership of Platon Kostyuk, has contributed so much to neuroscience, or maybe it was the location in Kiev, one of Europe's most architecturally rich and beautiful cities situated on the Dnepr river, or perhaps it was the enticing social events – whatever, the fact remains that we were fortunate enough to assemble a first class programme of more than a dozen speakers from across Europe and the USA. But what about the student delegates – will anyone actually attend our event? Again, we need not have worried as the response to our call for applications was overwhelming and the quality of submitted cvs impressive. After much deliberation, a total of 45 postgraduate and post-doctoral student delegates were selected from Institutes and Universities of UK, Ukraine, Romania, Slovakia, Russia, Italy, Hungary, Bulgaria, Belarus, Czech Republic, Georgia and Brazil.

Now our thoughts turned to the workshop schedule itself and the practicalities of providing a stimulating scientific programme that combined both oral and practical elements. Where will we accommodate everyone, how shall we keep them occupied for the scheduled 4 days of our workshop? What about that other most essential ingredient – the social programme? We take our hats off to our co-organizers Oleg Krishtal, Nana Voitenko, Olga Lyubanova and Sergei Khasabov. Their unbounded enthusiasm and support for the workshop carried it forward and truly made it the success that it was. They made it feasible to run a workshop that delivered a series of 12 plenary lectures, 10 demonstrations and hands-on practicals, three poster sessions and a social programme that generated a real feeling of camaraderie amongst a group of people meeting, in many cases, for the first time.

The plenaries covered topics ranging from the peripheral neural encoding of pain, through to spinal or brainstem circuitry, regulatory processing and the challenge of analgesic drug discovery. Practical sessions provided the students with an insight to *in vitro* and *in vivo* methodologies, electrophysiology, light and confocal microscopy, behavioural physiology and molecular biology, as applied to pain research.

In the poster sessions, the students were able to present their own data and prizes were awarded to the best two posters. We acknowledge gratefully the support of Bill Willis (UTMB, Texas) and Ray Hill (MSD, UK) who enabled us to provide as prizes much coveted copies of the new edition of Willis & Coggeshall's *Sensory mechanisms of the spinal cord*. A book prize was also kindly donated by Platon Kostyuk for the best laboratory demonstration, as voted by the students. Interest beyond the confines of the Bogomoletz was evidenced by an invitation to hold a televised press conference with local media – questions on pain in the context of 'sado-masochism' were side-stepped as diplomatically as possible. But what of the social events? The unforgettable 'Walking tour of Kiev' that tested the stamina of many a delegate, the boat trip and BBQ on the beautiful river Dnepr with optional swimming and impromptu fireside concert, the fabulous suppers in traditional settings washed down with capsaicin-laced vodka followed by music, singing and (limbo!) dancing.

Many things contributed to the success of this workshop but may we take this

Top: Tombstone commemorating Oleg Bogomoletz, founder and original President of the Institute in 1953.
Above: Student delegates Andre Zaharenko (Brazil, white t-shirt, then clockwise) Mino Belle (UK), Lianne Leith (UK), Nadia Cerminara (UK) Charlotte Flavell (UK), Péter Szûcs (Hungary), Sergiy Lytvynenko (Ukraine), Aleksey Boldyryev (Ukraine), Volodymyr Cherkas (Ukraine), Stella Koutsikou (UK) gazing into the future?
Below, left: Participants and speakers assemble on the steps of the Bogomoletz Institute.

opportunity to say a huge 'thank you' to the speakers for giving up their valuable time to us, to all at Bogomoletz for the resources that were put at our disposal, to Physiological Society staff, especially David Bennett who efficiently attended to all manner of requests before, during and after the event, and finally, but not least, to the student delegates whose enthusiasm and energy for their science was tangible.

Bridget M Lumb
University of Bristol, UK
Anne E King
University of Leeds
Organisers

The host organizers perspective

Ukraine is gradually strengthening, both socially and economically, after a difficult period of political transition during the 1990s. Despite some progress, the financial climate for science and its future development remains austere, with government support still below perceived desirable levels. Bogomoletz Institute of Physiology in Kiev is one of only a few academic institutions that has not only managed to survive, but maintains a level of research that is scientifically

Below: Dmitrii Vasilenko (Ukraine) takes to the water during the river boat trip and BBQ.
Centre, top:: Enjoying the reception supper, co-organizers Oleg Krishtal and Nana Voitenko with Eugen Grishin (Russia).
Centre, below: Co-organizers Sergei Khasabov (USA) and Olga Lyubanova (Ukraine) take time out with Ray Hill (UK).
Far right, top: An impromptu sing-along sets the BBQ alight.
Far right, below: Organizers Anne King (UK) and Bridget Lumb (UK) enjoy a glass of wine with student delegates Dinu Crenguta (Romania) and Gayane Margaryan (Italy).

competitive and internationally recognized. Today, the Institute is a leading scientific research centre in Ukraine in the areas of molecular physiology, biophysics, neurophysiology and pathological physiology. In the context of allowing us to showcase to both the Ukrainian Government and the global scientific community our ability to conduct state-of-the-art research and to host international events, this workshop was extremely important. Without false modesty, we can state that the purpose of the workshop, which was to provide step-by-step methods and protocols of multidisciplinary approaches related to the study of pain transduction, was fulfilled. High attendance at all of the seminars and practical demonstrations by students, who had travelled to Kiev from many world famous laboratories, indicated that the areas of research covered by our workshop were sound. The vibrancy of the student poster sessions and many discussions between delegates testified to the quality and topicality of data they presented. The activity of the scholars suggested that the practical demonstrations had been worthwhile – even for those who were familiar with modern methods and approaches. We would like to thank all the Institute researchers who spent their valuable time preparing practical demonstrations that were interesting for all of the students from different areas of pain research. It was a real pleasure for the host organizers to recognize at the end of the event that our efforts were not in vain and that all our goals were accomplished. The utterance of Jürgen Sandkühler, one of our esteemed invited speakers, was among our rewards: 'I have put Kiev in my list of cities the invitation from where I will never reject!'

Oleg Krishtal
Nana Voitenko
Bogomoletz Institute of Physiology, Kiev
Co-organizers

Student delegate report

When I started my PhD, I had a lot of expectations about conferences. I thought of them as places where we could meet people working in the same field; and ask them for help and advice. However, after some years, I realized it was just not that easy. Poster sessions, and discussions between lectures, are just too short to meet everyone; and how can I find someone who I have read a lot about, but never seen? Generally, they are not the poster presenters and they clip their badges on their trousers where I cannot read their names, even with glasses. This workshop gave us the very opportunity to meet those scientists, who have the largest reputation in the field of nociception and pain research. We could learn a lot from their talks, get a very good overview of different areas of pain research, and see the theoretical background of different physiological techniques. Post-docs could learn how

Student delegate Volodymyr Cherkas (Ukraine) sharpens up his limbo dancing skills.

their professors thought about different topics and designed their experiments. Time for formal discussions was short, but we had time enough to talk to anybody during social events. Of course, I don't mean this could happen at the end of a 3 hour walk in Kiev, when nobody had air in his/her lungs except for the lady who was the guide! In The Bogomoletz Institute, we had a chance to see a lot of physiological and morphological techniques that are used in our field. Of course, 30-40 minutes are far too short to learn a technique but, at least, we got an impression and important information on who to ask if we want to do something similar. Everyone who demonstrated his/her own experiment was very enthusiastic and keen to do his/her best. We have had many nice social events, but my best memories are of the boat trip on the Dnepr river. During the trip we enjoyed a spectacular view of Kiev and the boat docked on a small island, with untouched habitat. It was quite cold, so Dmitri Vasilenko's swim in the Dnepr seemed a real miracle (I had two jumpers and a coat on!). While the Saslik (a grilled pork meat) was prepared, some guys made a fire, and that provided a very nice warm feeling. Ruslan Mazgutov had a guitar and started to play. It is time we thanked him for these moments. Many of the participants who knew these, mainly Russian, songs were singing along with him. It is hardly possible to describe the atmosphere which appeared in minutes and took me back to my teenage years. I would like to say many thanks for all the organisers and participants who made this workshop unforgettable for many of us.

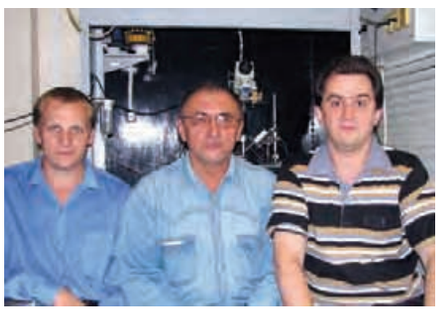
Zita Puskar
Semmelweis University, Budapest, Hungary
Delegate

Enigma of $P2X_3$ receptors: how to reconcile their properties with putative role in the nociception?

The receptors for ATP in sensory neurons are functional in homomeric ($P2X_3$) and heteromeric ($P2X_{2/3}$) forms. Which of them could be more important for nociception?

When locally applied to the tissues, ATP causes pain. The molecular basis for priming this sensation is provided by at least two types of receptors that open cationic (Na^+ and Ca^{2+} permeable) channels when bound to ATP. These receptors ($P2X_2$ and $P2X_3$, forming also heteromeric $P2X_{2/3}$) are expressed in the majority of sensory neurons belonging to dorsal root (DRG), trigeminal and nodose ganglia of mammals. The release of ATP apparently occurs when the tissue cells are destroyed or in response to deformation of hollow organs, when it is supposed to initiate visceral pain.

$P2X_3$ receptors are widely expressed in the small nociceptive sensory neurons. Their role in nociception has been revealed in numerous studies including knock-out experiments (Souslova *et al.* 2000) and various pain models. It seems to be especially prominent in inflammation. Recently our group has found that P2X receptors in sensory neurons and fibers are under opioid control (Chizhmakov *et al.* 2005).



Volodymyr Khmyz (left), Oleg Krishtal and Oleksandr Maximyuk

In response to extracellular ATP, $P2X_3$ receptors gate current that rapidly declines upon its onset, supposedly reflecting desensitization. In the case of sole activity of $P2X_3$ receptors (rarely observed pattern of response in the somata of DRG neurons), the residual steady-state current is virtually absent. The removal of desensitization is extremely slow. Various groups of investigators have reported that from 20-30 min are needed to obtain the next response of similar amplitude. This property of $P2X_3$ receptors results in at least two problems arising at different

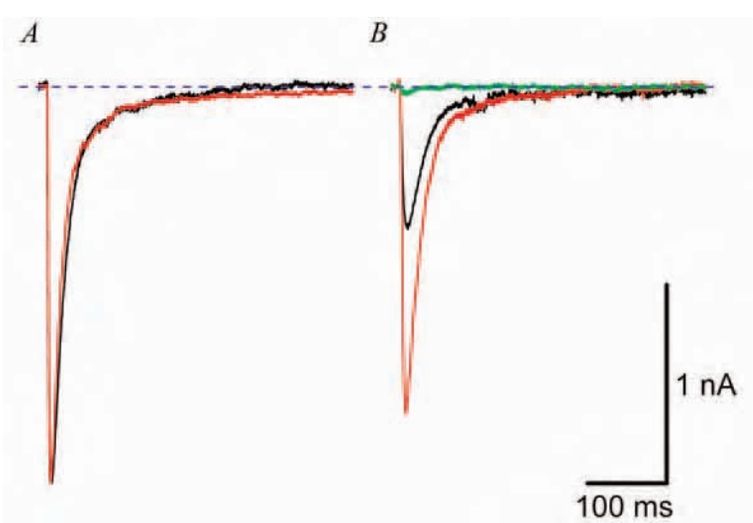


Figure 1. Response of a neuron acutely isolated from DRG of rat to externally applied ATP (100 μM, saturating concentration).
A, response elicited by a short (6 ms) application of ATP (red trace) is identical to the response elicited by a prolonged application of the agonist (black trace). *B*, the response recorded in 2 s after the short application of ATP is completely desensitized (green trace). The response recorded in 10 min after a short application (red trace) is still considerably desensitized, though it is larger than the response measured in 10 min after a long application (black trace).

levels:
- it is difficult to reconcile the desensitization removal being so slow with their putative role in nociception, and
- it is just difficult to study the function of these receptors.

The latter problem became obvious immediately after our lab discovered the ATP-sensitivity of sensory neurons: we tried to overcome it by removing ATP from the membrane before it would cause significant desensitization ('square-pulse' application technique (Kryshtal *et al.* 1982)). However, this approach, successful in eliciting perfectly reproducible responses of much slower $P2X_2$ and $P2X_{2/3}$ receptors, gave only partial relief in case of the most rapid $P2X_3$ receptors: it was impossible to make the square pulse of agonist application much shorter than 100 ms and this time was already sufficient to result in nearly complete decay of the response. Recently we returned to this problem by using piezoelectric drive of the microfilaments used for the application of ATP to the cell. This technique, introduced first by Dudel and colleagues, enabled us to apply ATP to the cell for the time as short as 4-7 ms (depending on the cell size), washing out the ligand just at the peak of response. We have found a remarkable picture: the kinetics of current decay appear to be completely independent on the presence of agonist at the membrane (Fig. 1*A*). This could indicate that the rapid decay of the response of $P2X_3$ receptors to ATP reflects deactivation, not desensitization. However, subsequent trial (in 2s after a short application of the agonist) demonstrates that the desensitization is complete (Fig. 1*B*). Correspondingly, our finding better fits another picture. Recently it has been demonstrated that the anomalously slow rate of desensitization removal roughly corresponds to the rate of unbinding of labelled ATP from the neuronal membrane (Pratt *et al.* 2005). The authors demonstrated that to be desensitized, the channel has to be activated first. When activated, $P2X_3$ receptor acquires a site which binds ATP on a long-term basis. The affinity of this site to ATP is high: use-dependent desensitization occurs in nanomolar range of background ATP concentration.

Thus, when bound to ATP, $P2X_3$ receptor is prone to activation and desensitization with a subsequent ultra-slow removal of the latter occurring via unbinding of ATP. Our experiments with rapid ATP removal seem to confirm this picture in its main details. Fig. 1*B* demonstrates that desensitization elicited by short application of ATP lasts for many minutes. Desensitization removal takes 15-20 min in the case of short application vs. 20-30 min for a long one. This slight difference may indicate a possible existence of several desensitized states.

Thus, our data suggest that the 'duty cycle' of an open channel gated by $P2X_3$ receptor negligibly depends on the presence of agonist after the latter has been bound by the receptor. Unfortunately we still know nearly nothing about the temporal pattern of ATP release/removal which occurs at the ATP-sensitive nerve endings *in vivo*.

Activation of $P2X_3$ receptors develops in the range of micromolar concentrations of the agonist, while their desensitization occurs at nanomolar concentrations. The background concentration of ATP in the tissues varies within this range of values in a function-dependent manner, reaching micromoles in the working muscles. Designed as they are, $P2X_3$ receptors should be sensitive to rapid acts of significant ATP release and remain silent long time after being activated. It remains enigmatic, how to reconcile this property of $P2X_3$ receptors with their putative function as nociceptors. Taking into account their most probable importance for this function (evidence from KO animals inclusive, see also (Cockayne *et al.* 2000)), it can be suggested that $P2X_3$ receptors are most important in their heteromeric form with $P2X_2$ receptors comprising a signaling unit which is "ever-ready" to generate long, weakly accommodating receptor potentials. According to our experience, numerous middle-size DRG neurons acquire robust rapid ($P2X_3$ receptor-mediated) response to ATP. Its functional role at the periphery may well be other than the nociception.

Acknowledgements

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Calcium disorders as a common denominator of different types of pain

Within the last period, more and more attention has been paid to disorders of calcium homeostasis. These disorders at least accompany many types of neuropathic and inflammatory pain, and it cannot be ruled out that such disorders are one of the reasons for the development of many pain-accompanied pathologies

Long term chronic pain, mainly inflammatory or neuropathic, afflicts about 25% of the general world population. More than 60% of people aged 65 plus complain of daily pains. This degree of disability has a huge economic toll in terms of loss of employment and disability payments, but quality of life is equally compromised. Pain is thus a major medical issue; it is not simply a sensation but an event that also triggers aversive and threatening psychological feelings. Patients in pain are likely to become depressed and anxious, have disturbed sleep patterns and generally have a poor quality of life. The importance of understanding the ways by which the central nervous system can alter incoming signals that relate to pain processing stimulated an increasing number of investigations, many of which are concentrated on two first elements in the pain pathway – dorsal root ganglion (DRG) and dorsal horn (DH) neurones.

Multiple, and possibly common, mechanisms appear to be involved in the generation of chronic pain on the level of primary and secondary sensory neurones independently of aetiological diagnosis of pain. Molecular mechanisms leading to changes in patterns of action potential generation in primary neurones, modification of synaptic transmission between primary central afferents and secondary dorsal horn neurones and spinal neurone hyperexcitability acting in concert contribute to the generation of chronic pain. In spite of a profound difference in patterns of changes or damage in primary and secondary nociceptive neurones the pain syndromes as observed in numerous studies conducted on different animal models are generally common. Thus, there is a reason to believe that multiple and common mechanisms may be present in chronic pain conditions of all aetiologies.

Calcium is a universal second messenger, and changes in the intracellular cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) triggers a wide spectrum of cellular responses, including a long-lasting modification of synaptic transmission and changes in cellular excitability that may lead to changes in the transmission of nociceptive stimuli. It has been shown in recent works originating from different laboratories that experimental chronic pain conditions (including peripheral inflammation, nerve injury and diabetic neuropathy) do induce significant changes in $[Ca^{2+}]_i$ regulation in DRG and DH neurones participating in transmission of nociceptive signals Voitenko *et al*. 1999; Voitenko *et al.* 2000; Huang *et al.* 2002; Kruglikov *et al.* 2004).

Thus, impaired cytosolic free calcium regulation may be a basis for abnormal nociceptive signalling during various types of diseases and pain syndromes. Moreover, we have shown that these changes in the calcium regulation are similar in DRG and DH neurones indicating that they might be general for many types of neurones from central and peripheral nervous systems.

Abnormalities in neuronal calcium homeostasis, which lead to impairment of nociceptive neurotransmission, have been detected in many pain models such as diabetic and nerve-ligation-induced neuropathies, carrageenan- and CFA-induced inflammation, cancer

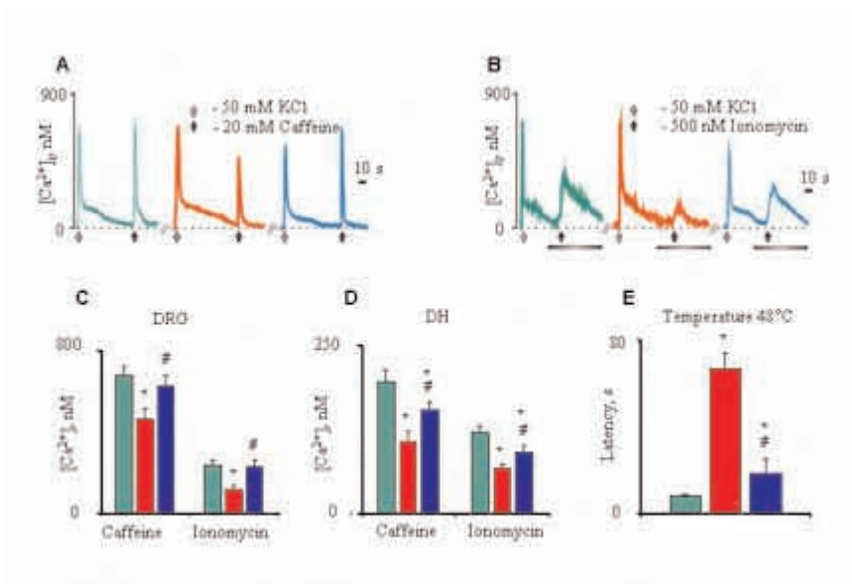

Figure 1. Nimodipine-induced restoration of calcium signaling and facilitation of diabetes-induced sensory abnormalities.
A and *B*, Representative examples of the effect of nimodipine treatment on amplitudes of $[Ca^{2+}]_i$ transients induced by application of caffeine (*A*) and ionomycin (*B*) in DRG neurons. The traces recorded from a neuron of control animal are shown in green, diabetic (red) and nimodipine-treated diabetic (blue). Grey bars in *B* indicate application of Ca^{2+}-free extracellular solution. *C* and *D*, Average values of amplitudes of caffeine- and ionomycin-induced $[Ca^{2+}]_i$ transients in DRG (*C*) and DH (*D*) neuronal preparations of control (green bars), diabetic (red bars) and nimodipine-treated diabetic (blue bars) rats. *E*, Hot Plate test: nimodipine treatment (blue bar) partially normalized thermal sensitivity in diabetic rats (red bar) as compared with control animals (green bar). Diagrams reflect a latency of nociceptive reaction at 48°C.
* $P < 0.05$ vs. control, # $P < 0.05$ vs. diabetic animals. In all experiments $n > 10$.

pain, etc. In particular we have shown an increase of Ca^{2+} entry to the cytosol via glutamate receptors in neurones of inflamed rats (Voitenko *et al*. 2004a); an increase of Ca^{2+} entry to the cytosol via voltage operated calcium channels in neurones of neuropathic rats (Voitenko *et al*. 2000); a decrease of calcium uptake and release by mitochondria (Svichar *et al*. 1998; Voitenko *et al*. 2004b) and a decrease in calcium mobilization from the different types of the endoplasmic reticulum (ER) calcium stores (Kruglikov *et al*. 2004; Voitenko *et al*. 2004b) in neurones of both pathologies. It is also important to emphasize that calcium abnormalities in these models are well correlated with the development of many pain-related symptoms such as thermal and mechanical hyper- and hypoalgesia and changed pain sensitivity, indicating a possible relationship between them.

The other corroboration of the calcium theory of pain is the fact that chronic treatment with calcium antagonists may be effective in both the restoration of calcium signalling in DRG and DH nociceptive neurones and the reduction of diabetes-induced sensory abnormalities. We have shown recently (Shutov *et al*. 2006) that treatment with the calcium channel blocker nimodipine was able to restore impaired Ca^{2+} release from the ER, induced by either activation of ryanodine receptors or by receptor-independent mechanism in both DRG and DH neurones (Fig. 1). The beneficiary effects of nimodipine treatment on $[Ca^{2+}]_i$ signalling were paralleled with the reversal of diabetes-induced thermal hypoalgesia and normalization of the acute phase of the response to formalin injection. Nimodipine treatment was also able to shorten the duration of the tonic phase of formalin response to a control value.

It should also be noted that at the moment there is no single theory which can explain the development of allodynia and hyper- and hypoalgesia during diseases of different aetiologies, as well as no unified point of view concerning the influence of altered calcium homeostasis on neuronal structures responsible for inpaired nociceptive synaptic transmission and induction of pain. Therefore any advances in the development of a unifying theory that may explain how different diseases result in common pain abnormalities look very attractive.

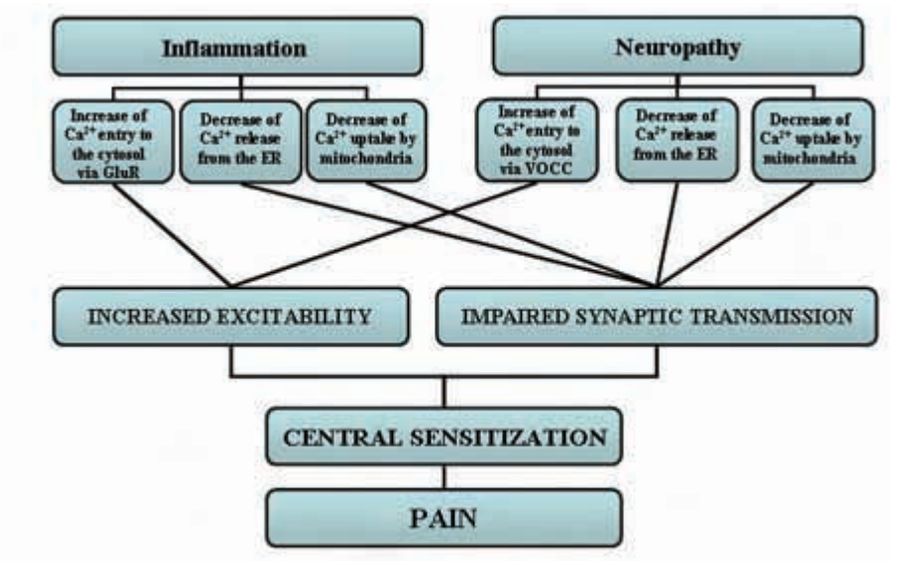

Figure 2. A simplified scheme of calcium theory of pain. An increase of Ca^{2+} entry into the cytoplasm together with decrease of Ca^{2+} accumulation by the ER and mitochondria lead to calcium overloading. That, in turn, results in hyperexcitability of nociceptive DRG and DH neurons and changes of synaptic efficacy between them. All together it might produce central sensitization and pain.

Based on many recent observations, including those mentioned above, we venture to suggest the following simplified scheme that might be a basis for this theory: increase of calcium entry via voltage- or ligand-gated calcium channels and/or decrease of accumulation of Ca^{2+} by the ER and mitochondria as a result of disease development lead to temporal or permanent calcium abnormalities. That, in turn, results in hyper-excitability of DRG/DH neurones and/or changes of synaptic efficacy between them. All together it might produce central sensitization and pain (Fig. 2).

Acknowledgement

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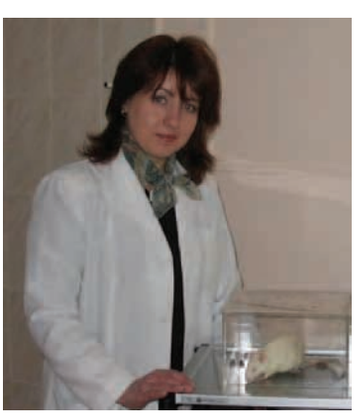


Nana Voitenko at work in the Bogomoletz Institute of Physiology.

THE JOURNAL OF PHYSIOLOGY

How to keep the loyalty of authors and readers

What is needed these days to keep a journal fresh and interesting to authors and readers? This question drove much of the discussion at the recent *Journal of Physiology* Editorial Board meeting in New York in September. At every meeting the Board reviews standards and Editors are encouraged to accept only papers that make an important step forward in their fields. In addition, for a number of years the Board has commissioned timely Topical Reviews in emerging new areas, sometimes associated with sponsored Symposia. More recently, recognising that progress in science is the result of robust and frank debate, Editors have discussed introducing features that involve an interactive element. Letters to the Editor were introduced in 2004 to enhance interaction with readers.

It has been acknowledged that young scientists in particular, and especially young American scientists, need to be reminded that *The Journal* is a dynamic and forward-looking publication.

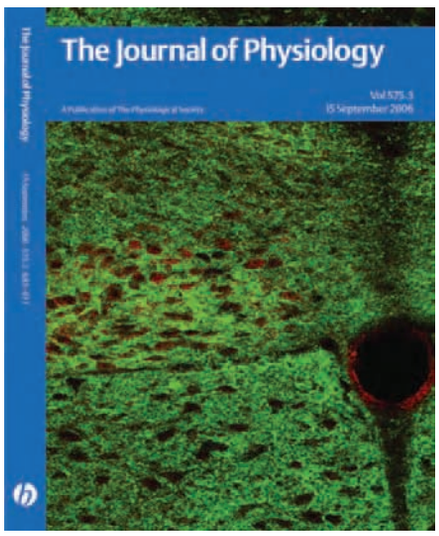
One aspect of *The Journal* that can deliver this message is the style of the title. Earlier in the year *The Journal*'s Executive Committee agreed that the title style was beginning to look very different from those of current competitor journals and that the elongated serif font emphasised the historical importance of *The Journal* rather than its current relevance. The title was last redesigned in 1994 when *The Journal* changed from monthly hardback issues to fortnightly paperback issues. In the intervening years *The Journal* has been increasingly challenged to maintain the loyalty of its authors and readers. With these thoughts in mind, the Executive Committee decided to incorporate elements of The Society's rebranding project (see p. 46) into a modernisation of *The Journal*'s title and the company that has undertaken the project, 35, was commissioned to produce a new title. After a process of consultation involving The Society, Editors and Blackwell Publishing, a new design was agreed and approved at the Board meeting (see example right). *The Journal* will continue to keep its by-volume colour scheme for the spine and this will form the background to the title and other front cover details, keeping them clearly readable and distinct from the background cover image.

The Journal is also introducing a new mini-review article type aimed at and for younger scientists. The model for this is the successful *J Neuroscience* Journal Club feature and this title will be adopted for the *J Physiol* articles to acknowledge the inspiration for the initiative and inform potential authors about the purpose of the article. Journal Club articles will be short reviews of recently published manuscripts and authorship will be limited to graduate students, post-doctoral fellows and other training level scientists. It is envisaged that these reviews would provide an appraisal/opinion of a manuscript published within the last two issues of *The Journal*, and will provide young scientists with an opportunity to hone their writing skills andintroduce them to *The Journal of Physiology* early in their career.

Other initiatives to attract readers and enhance the appeal of *The Journal* will be considered in the coming year.

Milestones for Publications Office staff

On 1 September this year Ann Watson, well known to all *Journal of Physiology* Editors and referees, completed 20 years on the staff of *The Journal*'s peer review team. Over the years Ann has seen many changes to the way papers are reviewed. She began work as a Distribution Assistant for Tim Rink, who was then one of the Distributing Editors (DEs) based in the Cambridge Physiology Department. She worked for four Cambridge-based DEs before moving to the Publications office at CUP in 1994, to form the nucleus, and eventual leader, of a team of Publications Administrators working remotely for the Distributing (now



Senior) Editors. The review process was paper-based long after type setting and copy editing went digital. Postage bills were enormous – £25K by the time that the online submission system was introduced. Paper and associated postage costs were only eliminated with the introduction of the Bench>Press online submission system in 2002 – which strangely enough cost exactly the amount saved in postage. The process of educating Editors in the use of the online system has sometimes been painful for both parties, but Ann has ensured that all but the most electronically challenged Editors have learned how to report online. Ann is committed to making the process of submitting a paper to *The Journal of Physiology* a positive experience. As one Society Officer recently commented, she makes being rejected seem almost a pleasure.

In November, another member of the Publications Office team, Linda Rimmer, will also reach her twentieth anniversary with *The Journal* and The Society. Linda began working for *The Journal* in November 1986, as a Publications Assistant in *The Journal*'s offices, which were then part of Cambridge University Press. The work involved coordinating the flow of submitted manuscripts between DEs and *The Journal* office. Linda has since gone on to work with six Chairs and one Editor-in-Chief. In 1988 she took on administration of the Editorial Board meetings and has organised around 40 Board meetings. In 1999 *Journal of Physiology* Symposia were introduced

Blackwell Publishing representative from Boston, Robert Harington with new Editor Daniela Pietrobon from Italy (above); Editor Stefano Vicini (below)

and these too have all been organised by Linda (pictured below with *Journal* International Editor Steve Mifflin). The success of these Symposia was recently acknowledged when The Society agreed to increase the budget so that more can be organised. More recently, Linda has become known to Society Members as the Executive Editor of *Physiology News*. In this role she is

credited with raising the standard of the magazine while reducing its production costs. She has also been instrumental in reviving The Society's Monographs Committee as the Biomedical Publications Committee, which is in the process of setting up a text book deal with Taylor and Francis, and producing many of The Society's publications.

The contribution of both Ann and Linda to *The Journal* and The Society over 20 years was marked by a presentation at the Editorial Board dinner.

Carol Huxley

(*photographs by Carol Huxley and* BuckandTipp.com)

Experimental Physiology
Translation & Integration

New Editors

Three new editors have been appointed with an interest in the field of Computational Physiology

George Billman

George received his Ph.D in Physiology and Biophysics from the University of Kentucky, Lexington, Ky. After the completion of post-doctoral training under the direction of H Lowell Stone at the University of Oklahoma, he joined the Faculty of the Department of Physiology at The Ohio State University in Columbus, Ohio. He is currently, a Professor of Physiology and Cell Biology there. His primarily research interest involves the investigation of the mechanisms responsible for ventricular fibrillation. He currently is investigating the effects of endurance exercise training on cardiac autonomic regulation and the susceptibility to ventricular fibrillation induced by myocardial ischemia.

Igor Efimov

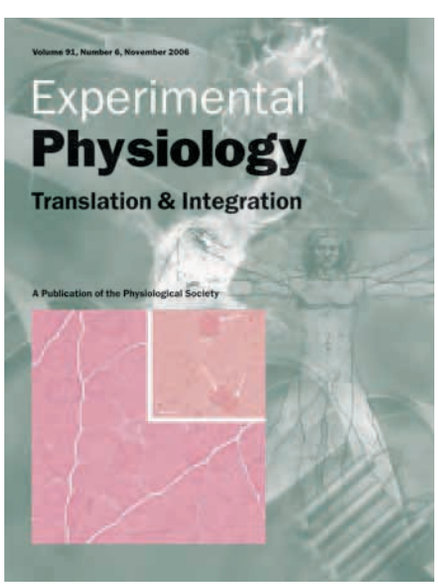
Igor is an Associate Professor of Biomedical Engineering, Cell Biology and Physiology, and Radiology at Washington University in Saint Louis. His research is focused on the mechanisms of cardiac arrhythmias and on development of antiarrhythmia therapies using implantable device approach.

His research laboratory employs and develops various optical imaging techniques to study action potential generation, propagation and failure, including fast fluorescent imaging with voltage-sensitive dyes, optical coherence tomography, quantitative immunohistochemistry.

Nic Smith

Nic is a University Lecturer and Fellow of St Johns College at the University of Oxford in Computational Biology. His research interests include the development of integrated computational models which span cellular through to tissue scales. His work is this area has focused largely on the heart and specifically the coupling of coronary blood flow to excitation-contraction under normal, acidotic and ischemic conditions.

November issue



Young scientists and the media

Like many scientists, I often get frustrated when I read or hear a science story in the media. For a long time, bad science in the media has been acceptable. Fortunately, however, things are improving. What can we do to help improve the situation?

Scientists and the media are both at fault, mostly due to the lack of understanding that exists between the two. This is where *Sense about Science*, a charitable trust who promote the use of scientific evidence in public debates, come in. Through their VoYS (Voice of Young Science) programme they run VoYS media workshops for early career scientists (post-doctoral fellows or equivalent in first job, and post-graduate students) which aim to give them an understanding of how the media works. I attended their most recent workshop in June with other early career scientists from the biomedical sciences.

The workshop consists of a series of panel discussions. Our first panel discussion was with a group of scientists who had spoken to the media on controversial aspects of science. They explained the problems they had faced and how they had dealt with them.

We then spoke to a group of journalists. For most of us this was our first experience with the media, and they explained how they approach a story, what problems they encounter, and the pressures they are under. The final discussion covered the communication of (preferably published) research to the media, the value of media training, and the importance of communicating accurate information to the public.

It was a highly informative and enjoyable workshop, directed at younger scientists, who tend to be in the lab more and are usually more nervous about talking to the media. We were encouraged to get more involved in scientific debates which we all agreed would help challenge the stereotypical image of scientists as well as ensure better science reporting.

Selina Pearson
Affiliate Member, University of Birmingham, UK

Sense about Science *has recently published a media guide based on their workshops called* Standing up for science *which can be downloaded from the web site* www.senseaboutscience.org/VoYS.

From molecules to behaviour

The Young Physiologists' Symposium took place alongside the main Physiological Society Meeting in July 2006 in sunny, bustling London. The meeting, *From molecules to behaviour*, brought together young investigators from all over the UK. Presentations covered diverse topics – from studies of ion channel structure and function through to fMRI of human subjects and, of course, food, alcohol and sex (*α-MSH and appetite for sex in hungry male rats* from Celine Cacquineau of the University of Edinburgh and *Evidence that ethanol equilibrates rapidly across the* C Elegans *cuticle* from Philippa Mitchell of the University of Southampton). The plenary talk, to an over-flowing lecture theatre, was delivered by Eve Marder (Brandeis University, Massachusetts). Together with Frances Edwards (UCL), Eve formed the panel for judging the presentations and participated in many discussions on science and on life as a scientist. The meeting also incorporated an insightful presentation given by Ted Griffiths (Director of the Biomedical Research Education Trust) on the need to deliver informed talks in schools on animal research, and gave participants a feel of how little unbiased information on such matters is currently available in schools. The meeting, of course, involved more than just science, and taking advantage of vast nightlife available in London, the participants enjoyed an evening of modern French food and drinks in a Spanish bar. The meeting concluded with prizes awarded to Clare Howarth (University College London) for the best talk and Nick Riddle (University of Cambridge) for the best poster presentation.

All in all the meeting provided a good opportunity for young investigators to present their work and meet many people at similar stages of their scientific career in a friendly atmosphere. We would like to thank The Physiological Society (especially Donna Brown) for giving us the opportunity and the means to host such a meeting as well as everyone in the Physiology Department at UCL who helped with the organization. Last but not least, thank you to all the participants. We hope to see you around!

Izumi Fukunaga
Clare Howarth
Rosemary Milton
Ede Rancz
University College London, UK

Shmma Quraishe (left) and Sarah Luedtke from Southampton University who participated in the YPS.

David Henry Smyth

Ian Roddie looks back at the distinguished physiological career of 'an adult white rat enterocytologist'

David Smyth was born in Lisburn in Northern Ireland in 1908 where his father was a primary school headmaster. After reading medicine in Belfast and a postgraduate studentship with Herman Rein in Gottingen he proceeded to a distinguished career in academic physiology.

It began with a lectureship at UCL with Charles Lovatt Evans. When war started in 1939, he was evacuated with part of the UCL medical school to Sheffield. Here he worked with the future Nobel Laureate, Hans Krebs, who summarised his character with remarkable astuteness: '*We all learnt very quickly to appreciate his exceptional qualities. Not only was he a very hard worker, he was also an original thinker, always helpful, very witty and humorous in his comments on day-to-day occurrences. Modest in his bearing and good-natured, he never complained. In spite of being busy he was never in a hurry or "flap" and always had time for kindness*.'

When the UCL School moved to Leatherhead in 1940, with FR Winton as Dean, David became Sub-Dean. In 1946 he moved to the Chair of Physiology at Sheffield where he remained until retirement in 1973. For his work on intestinal absorption he was elected FRS in 1967.

In all matters he set himself exceptionally high standards. Central to his philosophy was the need to concentrate in depth in one field rather than range over many.

Unapologetically, he described himself as 'an adult white rat enterocytologist' and defended his policy thus, '*I have tried to defend the position of the extreme specialist through the paradox that only he who looks deeply into one small problem really appreciates some of the universal generalisations that lie below. I believe this happens in life on the widest possible scale. The person who plays one game intensively and sticks to this may learn more of gamesmanship than the one who dabbles in many. The gardener who specializes in chrysanthemums or dahlias or roses will get greener fingers than the person who keeps the whole garden tidy. The best musicians have usually started and many continue to concentrate on one instrument. And if I may give another example from one of my own hobbies – pedigree dogs – the person who knows most about dogs in general starts by concentrating intensively on one breed. But perhaps I am only making excuses for the most selfish and yet perhaps the most fundamental of all urges – the urge to do well with all your heart and soul what you really love doing.*'

David Smyth – a hard worker, original thinker, witty and humorous, modest, good-natured and passionate about the Keeshond (pictured below).

David was passionate about rearing pedigree dogs, particularly the Dutch Barge Dog, the Keeshond. The Smyth name is still mentioned with near reverence whenever specialists talk of Keeshonds. On being congratulated when one of his dogs won second place at Crufts, he demurred saying it was a matter of disappointment rather than celebration – 'it's like getting a CBE when expecting a knighthood!'

University administration did not attract him but he was a natural choice as chairman for any committee whose length was always shortened by his brief and pungent summaries of evidence. His perceptiveness, good judgment and, not least, his ability to express himself clearly and directly made him one of the wisest counsellors and led to a four year stint as Pro-Vice Chancellor. Though bespectacled and relatively short in stature with a voice characterised by a stammer and pronounced Ulster accent, he was much in demand as a speaker. At Society dinners his wit, modesty, commonsense and humour were such that his audience gladly forgave any problems in delivery.

His skills and attributes were recognised widely by The Society. He was onetime Chairman of the Editorial Board of *The Journal of Physiology* (1966-68), Foreign Secretary of the Society (1972-79), Chairman of British National Committee for Physiological Sciences and the British delegate on the Council of the IUPS.

After retirement he continued work on intestinal absorption and busied himself with writing. He wrote eight 'Personal View' articles for the *British Medical Journal* that became famous for their wit and insight. He wrote a book, *Alternatives to animal experiments*, in 1978, and succeeded Sir William Paton as Chairman of the RDS. He was involved in drafting Lord Halsbury's *Laboratory Animals Protection Bill* and chaired the committee of the University Federation for Animal Welfare.

In 1979 colonic cancer was diagnosed. Though the surgery was deemed successful his condition deteriorated and he failed to recover. His many friends attended the funeral at Eyam Parish Church near his Derbyshire home.

Ian C Roddie
Honorary Member, London, UK

Next time, Liam Burke remembers his time in Bernard Katz's laboratory at UCL in the 1970s.

William Bayliss

The Bayliss-Starling Prize Lecture

The first lecture in this series was given by Sir Charles Lovatt Evans who had been Jodrell professor and head of the Department at UCL from 1926 to 1949. Entitled *Reminiscences of Bayliss and Starling* it was a beautiful account of a world long lost, even in 1963. The lecture was published by The Physiological Society in 1964 and I treasure my copy. I believe it was sent to all Members of The Society. The quotations below are from this published lecture.

I first met Sir Charles in 1958 when I was drafted into the RAMC and sent as a physiologist to Porton Down. He had retired from the Jodrell Chair at UCL and was head of the physiology section. He came in to the department some 3 days each week and invariably had tea or coffee and a chat in the lab in which I worked. So there were many stories about UCL, many of them scandalous. The obituary by I de Burgh Daly and R A Gregory is a charming and sympathetic account of his life (*Biographical memoirs of Fellows of the Royal Society* 1970, **16,** 233–252).

Lovatt Evans had worked with Bayliss and Starling from November 1910 when he had been an external candidate for the London University BSc in physiology and the practical examination was at UCL. Francis Gotch was the external examiner. Gotch asked Evans to stay behind as Starling wished to talk with him. Thus he met the staff and 'I was quite overcome by the natural friendliness of all these well-known people, and returned home agog with the exciting experience.' So Evans became Sharpey Scholar at £150 *per annum*. That must have been a substantial sum for those times. So began a new life at UCL.

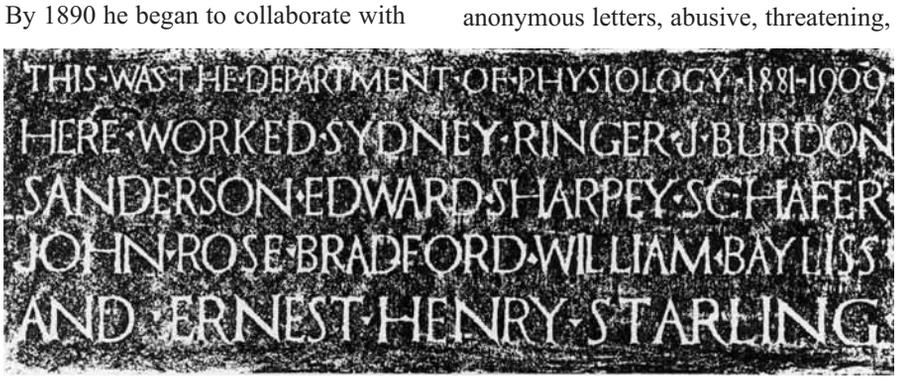
Bayliss was born in 1860, and Starling in 1866, so 1963 was the mid-point between their centenaries. Starling died at 61 and Bayliss at 64.

'Bayliss was well-to-do, but of simple personal tastes, and of the most gentle, retiring and kindly disposition. He had a large house in a 4 acre garden adjoining Golders Hill Park' where there was tea and tennis on Saturdays. He was married to Starling's sister. In a shrubbery between the two tennis courts was a small summer house where … one might find Bayliss surrounded by piles of penny exercise books, suggesting a marking of homework. This was in fact the preparation of the *Principles of physiology* … Close by was a laboratory he had built years before, and in which he afterwards made the photographs for the illustration of his book…'. This book, in the early editions, is a marvellous monument to his erudition. He had studied science at UCL and then as a medical student failed anatomy. At the oral examination the examiner said : 'your written answer to the question on the cords of the brachial plexus was extraordinary – wherever did you get it from?' To which Bayliss replied 'Well I never could memorize that sort of thing, so I put it the way I thought it ought to be.' By 1890 he began to collaborate with

Ernest Starling

Starling who was then at Guys. They 'were complementary. Bayliss was patient, over-modest and most genial. He radiated happiness and his talk was spiced with laughter. … his reading was vast and omnivorous.' With him it was not master and pupil, but two colleagues comparing notes. In 1922 he received an instruction 'to appear at Buckingham Palace to receive the accolade of the Order of Knighthood; he replied that as the date coincided with that of a Meeting of The Physiological Society, he would be unable to attend'. His priorities surely were right.

In 1903 he was involved with the anti-vivisectionists in what became known as the 'Brown Dog case'. He was accused of performing an experiment on a dog without anaesthetic. He won an action for libel, with £2000 damages, against Stephen Coleridge, which sum he gave to the college. Bayliss was exposed to 'the usual accompaniment of publicity, prejudiced press comments, and shoals of anonymous letters, abusive, threatening,



A rubbing of the plaque erected at UCL to commemorate the Institute of Physiology (courtesy of the Physiology Department, UCL)

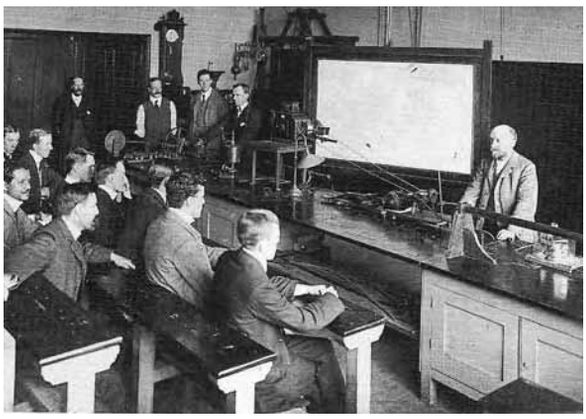
obscene or comical, the case must have been very distasteful to him at the time …'. The best account that I know of this case was written by Leonard Bayliss, son of W M Bayliss, *The 'Brown Dog' Affair* printed in a UCL Physiology Department magazine entitled POTENTIAL (Spring 1957, No 2, pp 11-22, UCL, Price 1/-). This piece is hard to find.

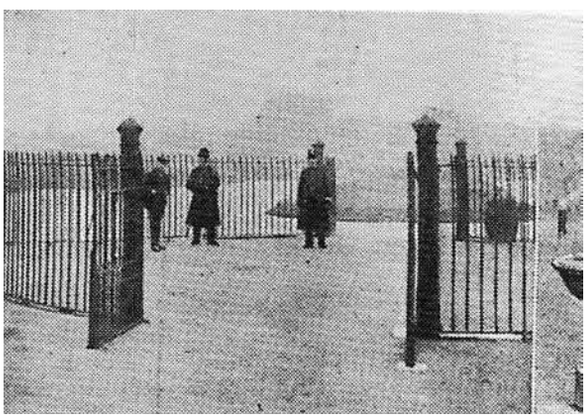
A bronze statue of a dog was erected in Battersea by the anti-vivisectionists to commemorate a dog. The statue was subsequently removed after attacks by medical students. The council was sued but the subsequent action went in the favour of Bayliss given the libellous nature of the inscription. The statue was erected in Latchmere Gardens and the cast iron fence around the area carried a sign in the 1980s saying, apparently without irony, *No dogs allowed*. Photographs of the re-staged experiment, of the statue of the dog, and of the location can be seen in *The world of UCL* by Harte and North (revised edition 1991, p. 127).

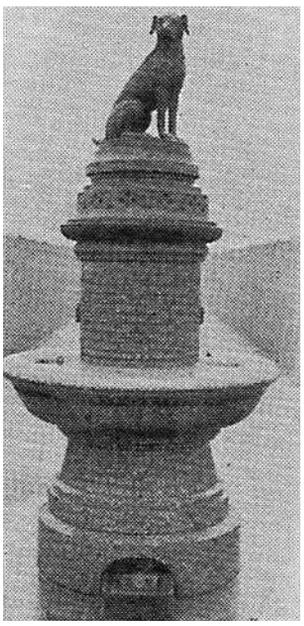
In contrast with Bayliss, Starling was 'brisk, ambitious, a bit quixotic, serious, generous and highly strung … he enjoyed the limelight, and the use of power, for good ends, but was too forthright and impatient to be diplomatic, though he realized that power lay that way … he enjoyed company, good wine and food, dancing and tennis, and was always keen on helping young people.'

'At the Physiological Congress in 1926, he (Starling) said that the British excelled in science because they were devoted to sports, and research was the greatest game of all. At which Gley, a small man with the voice of a bull, in an impassioned oration described France as "le berceau de la physiologie", and Pavlov spoke in German of his own invention.'

Starling's background was in medicine with the fundamental science added 'largely through his association with Bayliss, but the needs of medicine really formed the foundation of most of his work'. He was much influenced by Wooldridge at Guy's who advised him to work with Kuhne at Heidelberg. He







A reconstruction of William Bayliss' lecture used in the famous 1903 libel case (above, left); the 'Brown Dog' statue in Latchmere Gardens, Battersea, erected by the anti-vivisectionists (above, right); the site where the statue once stood (left).

was 19 years old at the time. From both Charles Darwin (an original Honorary Member) and T H Huxley (a founder Member) 'he drew the wide biological vision which characterised his writings, and from the second a keen interest in education and the desire to smite all humbugs – however big.'

He was elected to The Physiological Society 'on the same day as Bayliss, at the Annual Meeting at University College on 15 February 1890, Sidney Ringer in the chair'.

Starling, aged 33, went to University College as Jodrell Professor in 1899, the year of his election to the Royal Society.

And so the present Institute of Physiology came to be built. Before that the Physiology Laboratory was in the North wing of the College above the Slade School. It is commemorated at the top of the stairs in the front east corner of the Slade School. From the basement ascend nearly 75 steps to the second floor. There is a grey stone plaque with engraved inscription tinted gold on the wall to the rear. The inscription reads '*This was the department of Physiology 1881-1909. Here worked Sydney Ringer J Burdon Sanderson Edward Sharpey Schafer John Rose Bradford William Bayliss Ernest Henry Starling*'. G H Hardy would hae regarded this as forming the foundation of a very good first 11.

Starling was dissatisfied with this accommodation and there came to be built a large new department to be a nucleus of the new Faculty of Medical

The 2006 Bayliss-Starling Prize Lecture, *Annexin 1, glucocorticoids, stress and inflammation,* will be delivered by Rod Flower, FRS (William Harvey Research Institute, UK) (pictured right) at The Physiological Society Focused Meeting at the University of Bristol on Monday 4 December 2006.

Sciences. It was located on the land previously forming the playground of the University College School for Boys which moved to Hampstead. The building was completed within 1 year of going to the architect and with all equipment and fitting out cost ~£20,000. Large gilt letters on the front proclaim Institute of Physiology in an art nouveau style to be seen today. This was a tribute to German physiology institutes and 'much disliked by the then Provost, who thought he scented secession'. The building was very advanced for the time and in 1909 Starling wrote a *Description of the new physiology institute*.

Lovatt Evans summarised the joint work of Bayliss and Starling thus: 'The fruits of their labours have by now been homogenized into current knowledge, but the source of their enrichment should not be forgotten. The discovery of secretin was no doubt their most spectacular and fertile contribution, but even their first publication, on the electromotive phenomena of the heart beat, was of pioneer quality. Fundamental, if less dramatic, and bearing valuable, if late, fruit, were Starling's own work on lymph formation and on renal excretion, and the importance of Bayliss's investigations on membrane potentials needs no stressing in these days.'

The discovery of secretin and the coining of the name hormone, came about in an environment where the notion of chemical transmission was discussed. Oliver and Sharpey had published their work on the adrenal gland, and Eliot was contemplating ideas about the autonomic system. The time was right for their beautiful experiment and brilliant insight which opened up a whole new field of biological science, not only in medicine and physiology.

There was also Bayliss's work on the vasomotor system and his investigations of enzyme action, adsorption, and surface action. Starling introduced the heart – lung preparation and enunciated the 'law of the heart'. Starling published *The Principles of Human Physiology* and Bayliss *Principles of General Physiology*. 'Both books served to set the subject into its present mould.'

'Bayliss, the serene and devoted scholar, the true natural philosopher, Starling the man of action, with wide sweeping views; neither of them were subjected to the isolation of the specialist. It might be said that Bayliss and Starling flourished at a gestatory period in the history of physiology, a period in which, out of the fullness of time, the emergence of modern physiology was due.'

These lectures justifiably continue to honour them.

Tim Biscoe
Honorary Member, London, UK

A life of Ernest Starling

By John Henderson
2005, Oxford University Press. £35.99 (hardback)
ISBN 0 19 517780 0

When reviewing a biographical memoir, one is inevitably faced with the question of how much biographical information to include. In the case of John Henderson's entertaining life of Ernest Starling (1866-1927), published by OUP as part of a series sponsored by the American Physiological Society, Tim Biscoe's extended introduction to the Bayliss-Starling Prize Lectures above saves me the trouble, and can be consulted for details.

Starling is a fascinating figure. Although there is plenty of competition, he must be a leading candidate for the title of 'most important physiologist never to have won the Nobel Prize'. He was also never knighted, despite his pre-eminence and unlike many of his contemporaries. To learn why, read this book.

Henderson's book is enjoyable both for its glimpse into the past and for the contemporary parallels it tempts one to draw. Henderson recounts Starling's scientific achievements, and his collaborations and interactions with other scientific eminences like Bayliss, Charles Lovatt Evans and (later) A V Hill, and describes the early history of physiological research at Guy's Hospital and University College, the institutions where Starling spent most of his working life. The book follows Starling through all the phases of his career, including his war work in poison gas defence and his key influence on medical education in the London colleges.

Starling comes across in this book as a surprisingly modern figure in some ways, and often notably out of step with the more genteel tenor of the times. Tim Biscoe quotes Lovatt Evans, speaking in 1963 many years after Starling's death, describing Starling as 'highly strung' and 'forthright and impatient'. The book's picture of Starling bears this out, suggesting a man given to saying exactly what he thought, unvarnished, and without much regard for how it would be received. Through his outspokenness Starling seems to have had the knack of offending various establishments, medical, military and political, which almost certainly cost him a knighthood. Even when being complimentary Starling does not seem to have been the most tactful of men. The book describes how he recommended A V Hill, who he greatly respected, as his successor as Jodrell Professor of Physiology at UCL, but told the Dean that Hill [was] 'not a physiologist … of course' a remark clearly capable of being misinterpreted (the point was actually that Hill was something different, namely a biophysicist).

Starling also emerges as a believer in science as something that transcended national boundaries. Apart from the British physiologists who appear in the book, international figures of the time like Pavlov and Gleb Anrep also appear, testifying to the internationalism of physiological research both before and after the Great War. Like many of his contemporaries, Starling had trained in the laboratories of the great German physiologists of the late 1800s and was by his early 20s a fluent German speaker. He thus felt deeply betrayed when Germany went to war in 1914, penning wartime letters with scathing references to 'the Hun' and advocating the use of Mustard Gas as an offensive weapon. But after the war he seems to have felt that what was important was for scientists to get back to doing science, and he welcomed the German physiologists back into the fold and continued to publish in German journals. This forgiveness was not universal in science at the time, and may even have cost Starling the Nobel. But it gives a true flavour of the man and his principled, if rather black and white, views.

To sum up, John Henderson has given us a fascinating portrait of a great scientist, and a man of tremendous conviction, though poor political instincts. Readers will enjoy both the history and the contemporary parallels, and the book deserves a wide circulation.

Austin Elliott

Parliamentary and Scientific Committee

The July meeting of the Parliamentary and Scientific Committee asked the question 'is open access the future for scientific publishing?'.

The first of four experts presenting to the meeting, Mark Walport (Director of The Wellcome Trust), claimed that open acccess (OA) has arrived and is here to stay. Journals and learned societies must adapt. He stressed that the publication is an intrinsic part of the research process and should be funded in grants and that it would on average constitute 1% of a research grant. He also pointed out that submissions to the Oxford University Press experimental OA journal *Nucleic Acids Research* are holding up; authors are finding the money to pay the OA fee.

Robert Campbell (President of Blackwell Publishing), an advocate of gradual change in the publishing models, made the points that there are serious concerns about the OA author pays model. (1) There is the potential for a reduction in standards. Publication costs money and corners may have to be cut. Smaller journals will be tempted to publish more if article fees are their only source of income. (2) The barriers to readers may be lifted, but there will be barriers to authors who cannot afford to pay the fees. Access to the top journals will be confined to Northern hemisphere authors. (3) There is no evidence yet that OA publishing is viable. The Public Library of Science (PLOS) has recently raised the author fee for its journals to $2,500 and is still not able to balance the books, in spite of $13 million in donations. He also pointed out that variants of OA already exist: delayed OA, as exemplified by the society journals, whereby all content is free after a period, e.g. 12 months as is the case for *The Journal of Physiology* and *Experimental Physiology*; free access to developing countries through special agreements made with the publisher. He urged that proper research like the study proposed by RCUK should be conducted before forcing a change in the publishing model and pointed out that high quality journals would probably survive a subscription period of 6 months but lower quality journals would not and many society journals would be at risk. And he finally made the point that in the UK we have a very successful knowledge-based economy and that the industry behind this should be supported.

Ian Rowlands and David Nicholas (Centre for Information, Behaviour and the Evaluation so Research (CIBER) at UCL) reported on their surveys of author attitudes to OA and existing OA models. A recent CIBER author survey revealed that authors view OA differently depending on whether they are considering their own science or science in general . 74% agreed that high prices make access to journals difficult, but only 25% wanted to publish in OA journals; 48% agreed that too much science is published, but only 13% agreed that they publish too much. The survey found little interest in, or understanding of, OA among authors. Attitudes to OA were heavily dependent on discipline, age, funding and geographical location. 'Mainstream' scientists were generally Anglo-US based, ignorant, hostile and averse to change. 'OA enthusiasts' were largely young Asian, African or Eastern European clinicians, mathematicians, computer scientists or engineers. From the authors' point of view a single model does not suit everyone. CIBER also reported on their study of downloads from the OA journal *Nucleic Acids Research* both before and after the journal went fully open access. The journal site was opened up to Google in 2003 and this had an immediate effect on downloads from the site, which increased 143%. The subsequent increase in downloads when the journal went fully open access in 2005 was 8-10%. This suggests that the content that was previously not available via Google was not greatly missed and was presumably being accessed successfully by those who needed it.

The wide variety of views on the question of open access was made clear during the discussion after the presentations. If a researcher works in a well-funded institution in a well-funded discipline, OA does not present too many problems. For many it is not a realistic possibility; if the funding to pay author fees is not available, getting published will be a major challenge. Similarly, learned societies that rely on subscription income to fund their programmes will be challenged to replace that income. On the plus side for OA, it was noted that it allowed publication of negative results, which will restore the balance to clinical studies. And barriers to readership will be lifted. It was pointed out that researchers doing interdisciplinary work cannot access the information they need because their libraries cannot afford the full range of journals. Mark Walport mentioned that there are other ways of making content accessible that can co-exist with the subscription model. Some journals are experimenting with very cheap pay per view access models and societies might look at this as an alternative way to raise funds from their publishing ventures (although information from a recent HighWire Meeting suggests that these experiments are not raising much income). On the other hand, there are concerns about the model. Open access proponents assert that peer review will not be changed but lesser journals whose income depends on the number of articles published may be tempted to publish more. The barrier to readership will be replaced by a barrier to authorship; either way subsidies are required to ensure that the research output is published and is available to all who require it. Giovanni Mann spoke to the meeting about The Physiological Society's role in training young physiologists and how this would not be sustainable if the subscription income from the journals was lost. Mark Walport responded that The Society should apply to The Wellcome Trust for a training grant. Of course, the present costs of Society programmes for training young scientists far exceed the amount The Wellcome Trust are likely to grant. I believe Giovanni is framing his reply.

Carol Huxley

Parliamentary Links Day

The Royal Society of Chemistry's (RSC) Parliamentary Links Day on science and globalisation held on 27 June was an impressive event. Chaired by Brian Iddon MP, it was very well attended by Parliamentarians and representatives of the scientific community. Our new Chief Executive Mike Collis sat with Sir Geoffrey Howe (now Baron Howe of Aberavon), and the whole event was certainly an insight into what can be achieved by a learned society with enough clout – perhaps something similar might be considered under the umbrella of the BSF in future years.

The opening address was from Margaret Beckett MP (Secretary of State for Foreign and Commonwealth Affairs). She commended the occasion for being the most important scientific event in the Parliamentary calendar. She felt that Britain's standing abroad was very much linked to our status as a scientific nation, but the global scientific landscape is shifting with the emergence of India and China as being possibly the next knowledge superpowers. China has trebled its spending on R&D in the last few years and India now produces more science graduates than the whole of Europe. This could be a positive development for Britain if we seek to fully engage with them and build new collaborations. Science thrives on diversity. The Foreign and Commonwealth Office (FCO) Science and Innovation network of attachés posted around the world is poised to help us build these collaborations.

Simon Campbell (President of the RSC) stressed that the RSC was not UK centric in its outlook and wants to be the most effective international organisation for advanced chemical science. Various initiatives help them do this. They publish about 45 leading textbooks every year, hold international joint meetings with the help of the FCO, have made their journals free to all African scientists, produce education materials for the developing world and have an initiative called Chemistry Aid. He highlighted some of the potential threats to R&D. Dominance of Eastern low wage economies could undermine manufacturing industry in the West. Politicians have sometimes looked to the service sector to plug economic gaps left by the decline of manufacturing, but service industries cannot be expected to invest in R&D in the same way as manufacturing. Over-regulation in Europe and the USA, for example REACH, might also drive companies eastwards, places like Singapore which are now investing heavily in R&D and infrastructure will be only too happy to attract them. Companies like Government support, access to an educated workforce and sensible tax regimes. It is vital that the UK provides this sort of environment to encourage inward investment.

Robert Kirby-Harris (Chief Executive of the Institute of Physics, IOP) said that physics is a major force for development, e.g. through education work in the developing world. It is a core underpinning discipline for industry and medicine, for example magnetic resonance imaging and materials for transplants. The UK leads the world in laser physics, non-linear optics and photonics. The IOP has made a serious investment in its international activities. They have offices in China, Japan and Russia. Their education projects include funding mobile labs in a lorry which tours Africa introducing science to young people, setting up training programmes in entrepreneurship for developing countries and supporting relevant African learned societies to create a pan-African network.

Alan Malcolm (Institute of Biology) presented a case history of a very controversial area of science and globalisation – GM crops. He made the point that this could be viewed as both a failure and a success. A decade ago, the technology had hardly impinged on the international scene, now over one million square kilometres are under GM cultivation. Momentum in this area is considerable – more than 50% of soya produced worldwide is now GM herbicide tolerant, and about 25% of maize is GM insect resistant. The technologies are very popular and widely applied in China, India and the USA, but with almost no uptake in Europe through inadequate addressing of consumer concerns and political pressures. His conclusion was that the globalisation of science would continue in spite of Luddites in some regions, and that what had proved to be true for GM crops would also apply to other potentially controversial technologies such as stem cells. New technologies have to be effectively managed rather than resisted.

Dame Julia Higgins (Foreign Secretary of the Royal Society, RS) stated that the RS very much views itself as an international organisation. It actively recruits foreign members, and provides funding to stimulate international collaborations including engaging academics worldwide on major policy issues. The RS spends about £7 million per annum on international interactions, including a programme of international lectures, an MEP Pairing Scheme for young scientists (based on the very successful UK MP Pairing Scheme) which aims to increase awareness of science in the European Parliament and an understanding of Brussels amongst scientists. The RS has been very active in tackling development issues including input to the G8 2005 joint statements on Science and Technology for African development, and has been very vocal to the Department for International Development (DFID) on the role of science in eliminating poverty in Africa and elsewhere. Africa is a priority for the RS at the moment. They are strengthening the role of African science academies to provide advice to their Governments in partnership with the Network of African Science Academies, are launching a new grant scheme for partnerships between UK and African scientists to promote capacity building in the developing world, and have funded several African academies to become members of the International Council of Scientific Unions (ICSU).

Peter Saraga (Royal Academy of Engineering) gave a personal perspective from his experience of working globally for Phillips. Industry needs to combine the best of global

science and technology to create globally marketable products. Global businesses looking to access the best talents are looking towards Asia, for example Phillips is locating more of its R&D in China, but they are still investing in good R&D in the UK. Successful knowledge transfer is based on user needs and he noted the emergence of a new trend in international collaboration towards open innovation, with more emphasis on sharing knowledge as a route to success rather than the more secretive intellectual property route.

Zhiyong Jin (First Secretary for Science and Technology at the Chinese Embassy in London) talked about Chinese Government emphasis on international co-operation in S&T development. The Chinese economy is booming and is becoming very dependent on S&T. Chinese S&T development and reformation of the S&T system is directed by three main strategies, in human resources, patents and standards. They are looking to strengthen audit and evaluation of research, develop new science policies, laws, regulations and public science engagement. They are promoting knowledge transfer by new S&T intermediaries and incubators and high tech industrial development zones. The Chinese are now very keen to support international scientific collaboration and have signed inter-governmental S&T agreements with 96 countries, including the UK. There is a biennial China-UK S&T Joint Commission Meeting which promotes collaborations and seeks to remove obstacles. His presentation was followed by Jason Hahn (Science and Technology Counsellor of the United States Embassy), who noted that international science promotes the values of free societies and respect for diverse views, and is essential in tackling issues of global concern such as climate change and epidemics.

Phil Willis MP (Chair of the House of Commons Select Committee on Science and Technology) commented that international co-operation in S&T is now of vital interest to Parliament. Science is about picking a route through uncertainty, and politicians need to be engaged in global science that addresses global concerns such as energy supplies and climate change. He noted that there is still a problem of scepticism and ignorance about science amongst some parts of the general public, and gave perceptions of animal research as being a particular issue. He concluded that MPs have a key role to play in maintaining public confidence in science.

Sir David King (Government Chief Scientific Adviser) ended the session by highlighting that science and innovation was expected to play a key role in the wealth creation agenda supporting vital services such as pensions, education and health. The success of S&T has been amply demonstrated through increased life span and an explosive growth in world population. How we manage this in a limited resource environment is the big challenge for 21st century technology in water and energy, health, medicine and other key areas. This is a big opportunity, and the Government is looking to support the UK as the partner of choice for international scientific collaborations. He noted that the Government's Foresight processes had changed to get scientists and social scientists to work together to tackle major issues such as flooding and coastal defence. Other Foresight exercises that he mentioned included brain science, addiction and drugs, the determination and identification of infectious diseases and tackling obesity.

The session was wrapped up with a few complimentary remarks by Mark Lancaster MP, the son of the famous firework maker the Reverend Lancaster, who was apparently in the audience. Alas, no firework displays were available on the day but they consoled us with a good buffet lunch. I was left with much food for thought on ways of developing our Society's international activities and input to Government policy. Amongst other things that I will be investigating in the forthcoming months will be how we can get our scientists involved in Government Foresight exercises and other policy development activities. Members with any ideas about this are more than welcome to contact me.

Liz Bell

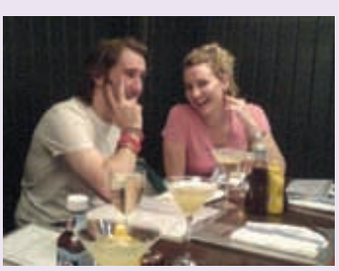
Introducing Affiliate Representative Lisa Mullen

Lisa Mullen (above) became an Affiliate Representative on The Society's Council in May and will serve a 1 year term. Originally a secondary school teacher, Lisa undertook an MSc in physiology and then went on to complete a PhD, graduating from Birkbeck, University of London in 2004. Lisa is currently a post-doc at University College London. She sits on Council, representing the views of Affiliate Members and has yet to attend her first committee meetings this autumn. She can be contacted by email on l.mullen@eastman.ucl.ac.uk.

Staff update

David Bennett (Events Administrator, International) and Heidi Adnum (Events Administrator, UK) (below) have recently joined The Society's Events Team. Elfa Wilmot has been made a permanent member of staff (responsible for human resources, the Benevolent Fund and travel grants), and Gabina Alfonso has been appointed as full-time Finance Administrator.

Heidi can be contacted on 020 7269 5715 (hadnum@physoc.org), David on 020 7269 5712 (dbennett@physoc.org), Elfa on 020 7269 5713 (ewilmot@physoc.org) and Gabina on 020 7269 5710 (galfonso@physoc.org).



Governance for beginners – the structure of The Society

The organisational structure of The Society's governance can be a mystery to Members. This article aims to explain in simple terms how The Society is run and how the decision making process works.

Council of Members/Trustees

At the heart of the organisational structure of The Physiological Society is the Council. All major business of The Society is directed by the Council, which currently meets 3 times a year.

Council Members are Trustees and, as The Society is a charitable company registered with Companies House, also Directors of the company. Trustees are legally responsible for the overall management, finances, administration, policy and strategic planning of The Society, ensuring that the charitable objectives for which it has been set up are met.

The Council consists of:

- a President, elected by the Council
- one Member elected by the Editorial Board of *The Journal of Physiology* (normally the Editor-in-Chief); and
- Members nominated by the membership or by the Council and elected by the membership at the Annual General Meeting.

Elections to the Council take place each year at the AGM, and any member of The Society is eligible to stand. Council Members are elected to serve for a period of 4 years. The current size of the Council is 23, but is being reduced to 20 as approved at the AGM in 2005. Meetings of the Council are chaired by the President.

In addition to Trustees, there are other invited attendees at Council meetings. They contribute to discussions, but do not vote. These are currently:

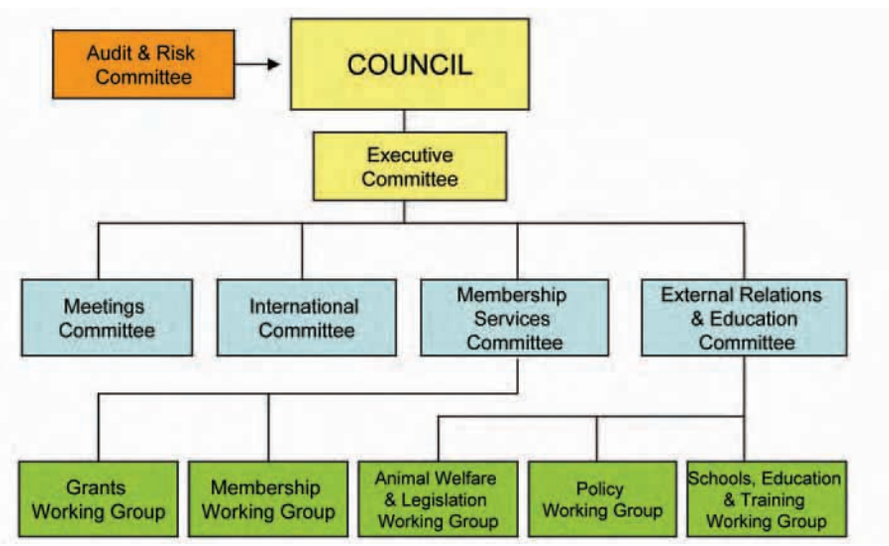
- two Affiliate representatives, nominated and elected by Affiliates
- Chair of the Editorial Board of *Experimental Physiology*
- Editor of *Physiology News*
- Chairman of the Heads of Department Committee

Administrative support is provided to the Council and its Committees by The Society's staff based in the London and Cambridge offices.

Executive Committee

The Council delegates the day-to-day management of The Society to the Executive Committee, which meets frequently throughout the year. Members of the Executive Committee are drawn from, and elected by, the Council.

There are seven members of the Executive Committee: the President of The Society, a Chairman, a Vice-Chairman, a Treasurer, a Meetings Secretary, an International Secretary, and the Member elected by the Editorial Board of *The Journal of Physiology*. The normal term of office on the Executive Committee is 4 years.



Current Committee structure

The 23 Council Members/Trustees

Jonathan Ashmore, Doug Corfield, David Eisner (International Secretary)*, Valerie Gladwell, Paul Greenhaff, Sarah Hall, John Hanrahan, Patrick Harrison, Anne King, Prem Kumar (Meetings Secretary)*, William Large (Editor-in-Chief, *The Journal of Physiology*)*, Graham McGeown (Treasurer)*, Ian McGrath (Chairman of the Executive Committee)*, Stafford Lightman, Clive Orchard (Vice-Chairman of the Executive Committee)*, Ole Petersen (President)*, Christof Schwiening, Sergey Smirnov, David Sugden, Alexei Tepikin, Keith Thornbury, Teresa Tiffert and David Wyllie.

* members of the Executive Committee

Committees and Working Groups

The Council also has Committees and Working Groups to which it delegates powers, and these groups report back to the Council. Membership of these Committees and Working Groups is drawn from the Council, but can also include other invited members. The Society's Committee structure is currently under review by the Executive Committee.

Audit and Risk Committee

The Audit and Risk Committee was set up to meet the requirements of good practice suggested by the Charity Commission. It reviews the effectiveness of internal financial controls and risk management systems, the effectiveness of our internal audit functions and the clarity and completeness of disclosures in the financial statements. The Committee consists of non-Executive Council members as well as invited external members.

Simon Kellas
Committees and Office Manager

For more information visit The Society's web site at http://www.physoc.org

Society rebranding

As you can see from the images pictured (right) The Physiological Society has been represented by what can only be called a mixed bag of brands (used in the loosest sense!) over the years. Whilst some may argue brand doesn't really matter to a society like ours and shudder at the mere thought of 're-branding', a small group of staff and Members thought differently, and sat down to review all Society publications – literature, stationery, and promotional materials. It should be possible to tell at a glance that something comes from The Society. Think BHF, Wellcome Trust … Our conclusion was simple – there was just no consistency: logo, typeface, colour, imagery … the list goes on.

We agreed that we should contact organisations that had themselves recently re-branded, and, not surprisingly, we found that their new looks were courtesy of several highly recommended communications agencies. Initial consultations with three of these agencies concluded what we already knew – that we were all over the place when it came to branding and to increase the presence of The Society we needed to do something about it.

Branding isn't just a logo, something we could draw on a beer mat at the pub; it covers all aspects of visual communication and ensures that our presence is clear and easy to understand no matter where or how it's being used. A brand also needs to be easy to apply with clear guidelines for all users, which in the long-term saves time and money.

There are many reasons why we want to increase the presence and recognition of The Physiological Society, all of which will benefit our current membership, but one of the primary reasons is to ensure physiology is a recognised discipline in years to come. Many 6th form students haven't even heard of the word physiology (despite physiology forming a large part of the biology curriculum) and physiology departments are rapidly being swallowed by the trendier 'biomedical sciences' or such-like.

Advancing the Science of Life

The Physiological Society

The concept of branding was presented to the Executive Committee and it was agreed that the recommended agencies should be invited to tender. Surprisingly impressed by the presentations, Exec invited the preferred agency, 35 Communications, to present to Council who, after lengthy discussion, gave the project the green light. (I should perhaps point out that this is a simplified version of events which in fact took 6 months to conclude.)

Over the next 6 months the brand was developed. The first step was to research what The Society represented so 35 interviewed numerous stakeholders over several weeks. The findings which were presented to Exec are summarised in the table (right).

Happy they had an accurate view of The Society's role and core values, 35 developed numerous different concepts which they presented to a group consisting of Exec and other interested parties. The group was very impressed with many of their ideas which were separated under four headings (exploration, inspiration, knowledge, quality and heritage) and under each of these at least four designs relating to the particular title. Two concepts were selected for further development and these were sent to Council for comment.

Making a final decision on which logo/concept should represent The Society was not easy. Although there was a significant majority of votes for the concept we selected, and indeed for the colour palette, trying to get everyone to agree on miniscule details like the final shape and position of text on the logo proved challenging, as, at the end of the day, everyone sees things differently and it would appear most people (particularly Exec members) think they have a flare for creativity. With guidance from 35 and our aims in mind we finally selected the logo and strap line you see (left). Obviously this project hasn't just been about the logo and strap line, many new materials will filter through our various channels of communication, so all I can really say is 'watch this space'.

Our new look will be launched early in 2007 in parallel with our new interactive web site. If you have any comments either now or when you see everything in place please feel free to contact me (dbrown@physoc.org).

Donna Brown

Perception of The Society

Role
- Support our Members
- Support scientists
- Promote physiology to schools and students
- Support and encourage physiology
- Influence government and opinion formers
- Promote the discipline and explain its importance

Vision
- To be financially sound
- Provide quality and value to Members
- Ensure subject remains relevant and recognised
- To be more a voice of influence
- Professionally led, strong Society
- Increase public understanding of science

Perception of identity
- Everything is inconsistent
- Not attractive to a younger audience
- What identity – we haven't got one!
- Our identity has no lasting recognition
- The old dog must go – irrelevant, too lengthy to explain

Perception of current communications
- Needs to be more engaging
- Quality is varied and there is no system
- Everything we produce is different
- Communications are generally patchy and inconsistent
- Web site needs to draw in the younger members of the scientific community
- Good content – could be presented better

Copy for the Spring 2007 issue of *Physiology News* should reach the Publications Office by 21 December.
Please send contributions to lrimmer@physoc.org

The Physiological Society — Scientific Meetings Calendar 2007

Meeting	Place	Date	Type	Abstract submission & Registration opens	Abstract submission closes	On-line Programme available	Published as Proceedings of The Physiological Society	Travel Grant Application Deadlines (Members & Affiliates)
Perinatal Physiology: From Uterus to Brain	Edinburgh	12-13 Feb	Focused	1 Nov 06	16 Nov 06	12 Jan	Yes	31 Dec 06
Ion Channels and the Microcirculation	Belfast	4-5 Apr	Focused	18 Dec 06	11 Jan	7 Mar	Yes	31 Jan
Endothelium: the Determinant of of Cardiovascular Health or Disease	Krakow, Poland	9-12 May	International Workshop	1 Jan	1 Mar	1 Apr	No	31 Jan
LifeSciences2007	Glasgow	9-12 Jul	Main	1 Jan	26 Feb	Apr	Yes	31 Mar
Cardiac Electrophysiology: With a Special Celebration of the Centenary of the Discovery of the Sinoatrial and Atrioventricular Nodes	Manchester	5-6 Sep	Focused	11 Jun	28 Jun	15 Aug	Yes	31 Jul
Joint International Meeting of The Physiological Society, The Slovakian Physiological Society and FEPS	Bratislava, Slovakia	11-14 Sep	Joint International	15 May	15 June	Aug	No	31 May
Molecular Physiology of Membrane Transport and Cellular Signalling	Lviv, Ukraine	18-23 Sep	International Workshop	1 May	1 Jul	1 Aug	No	31 Jul
Renal Cortex: Physiological Basis of Glomerular and Tubular Diseases	Bristol	17-18 Dec	Focused	10 Sep	27 Sep	19 Nov	Yes	30 Sep

Other key dates:

Date	Activity	Deadline (if applicable)
1 October 2006	Call for 2008 Main Meeting (Cambridge) Symposium Proposals	31 December 2006
1 January 2007	Call for proposals to host 2008 Focused Meetings *(Unsuccessful applications will automatically be entered for consideration in the next round)*	28 February 2007
February 2007	SIG Convenors Meetings	
1 March 2007	Call for proposals to host 2009 and 2010 Main Meeting *(Unsuccessful applications will automatically be entered for consideration in the next round)*	1 June 2007
March 2007	Meetings Committee / International Committee meetings	
October 2007	Meetings Committee / International Committee meetings	

Non-Society Symposium Grants
(max £1,000 each)
Deadlines in 2007
31 March
31 July
30 November

Special Symposium Grants
(max £5,500 each)
x 4 awards
Deadlines in 2007
At least 2 months prior to event
(for symposium in 2007)

www.physoc.org

THE LISTER INSTITUTE OF PREVENTIVE MEDICINE
ESTABLISHED 1891

LISTER INSTITUTE RESEARCH PRIZES

September 2006

The Research Prizes, valued £200,000 each, will be available from October 2007

THE LISTER INSTITUTE of Preventive Medicine is a registered charity established to support biomedical and related research and its membership includes some of the most distinguished bio-scientists in the UK.

The Institute now invites applications from outstanding **young researchers** in biomedical or related biological sciences for its 2007 Research Prizes. Awards will be made on the basis of the originality, quality and potential significance of the research and on the achievements of the applicant.

The applicant's research proposal must explain how the award will help them pursue their independent research interests. Prize Winners will receive **£200,000** which may be used **in any appropriate way to support their research**, other than the provision or augmentation of personal salary. However the monies may be used **to free the recipient from teaching or administrative duties** by funding a replacement lecturer etc. Expenditure of the award may take place over a period of up to five years.

Candidates must have more than three and less than ten years' post-doctoral experience on 1 October 2007 and must have guaranteed employment for the first three years of the notional years of the award in any not-for-profit institution which might be a university, charity-funded institute or Research Council Unit. The bulk of the research must be conducted in the UK but the awards are transferable between institutions in the UK.

Application forms and further particulars may be obtained from the Administrator of the Institute
Telephone/Fax: 01923 801886
Email: secretary@lister-institute.org.uk
or via the Institute's Website:
www.lister-institute.org.uk

Completed forms must be returned not later than 5 December 2006

Sir Joseph Lister courtesy Royal Veterinary College

BIOSCIENCES FEDERATION

The BSF has grown in strength during the summer months. This is because we have made two important appointments to help with the policy work. First, we have recruited Caroline Wallace. She will have particular responsibility for our Animals Science Group and our European Liaison Group. Caroline has a PhD in molecular biology and has worked with us for the last two years in a contract/consultancy role. The second appointee is Richard Bateman. He has resigned from a senior position at The Natural History Museum to become our Head of Policy in a part-time capacity. With his background in systematics and plant science he will increase the width of our 'in house' skill base. These important appointments have become possible because of increased membership and, importantly, a substantial voluntary increase in the subscription paid by several member organisations. As a consequence of these appointments we will be even more effective than hitherto in reacting to Government and other enquiries and initiatives. More significantly, we will be able to be more proactive. That is, we can start to identify initiatives as they are born and influence their gestation, and also give birth to some ourselves. In this context, the BSF will look to you, the member organisation and the individual, to help with horizon scanning and the identification of areas where we should take the lead.

Have you seen our response to the Cooksey enquiry? If you haven't, it is on our web site and it gives you some idea about what we are doing for you. I am sure you know that Cooksey is concerned with putting the funding for NHS Research and Development under the same umbrella organisation as MRC grant awards. Following our submission, the BSF was invited to a meeting with the Cooksey team to discuss four questions. In summary, these can be distilled down to two points. They were about translation (the conversion of world class science to medicines and improved clinical practice) and the incentives to offer scientists, departments and universities

Emma Southern, Head of Communications (top) and Caroline Wallace, Policy Co-ordinator (above), who takes on responsibility for the BSF Animal Science and European Liaison Groups.

in order to achieve this goal. We sat at tables of eight and took it in turns to give our answers to the questions. Interestingly, the answers reflected a broad swathe of agreement that both translation and incentives were not only desirable but essential. However, we did not tackle what I believe to be a central concern for the BSF. That is, under which *modus vivendi* will the new joint fund operate? Will it be that of the MRC or that of the NHS. We are absolutely clear about this question: it has to be that of the MRC. We should only give grants for potentially excellent world class research. If areas need strengthening we should not pretend that the science is excellent in order to make an award. If the country needs to strengthen an area then earmarked funds should be used for this explicit purpose. The marriage of funds for world class research and capacity building generally reduces the integrity of awards for both.

By the time that you read this we will have submitted our views about new RAE metrics to the Department for Education and Skills. The BSF strongly holds the view that a metrics only approach to the RAE after 2008 is wholly undesirable. The Federation takes the view that metrics should be there to guide and inform panels but we cannot imagine a suitable series of stand alone algorithms for dealing with all the complexities and different emphases across the biosciences. We also hold the view that metrics should not only be about inputs (for example, grant income) but also about outputs (for example, citations). However, the key element is that metrics are assessed by people and not software.

How do we undertake these policy reviews? From this summer we have developed a closer relationship with your Society in order that we might work together more effectively on key policy issues for the biosciences. As an issue comes to the fore, we write to all Member Organisations and ask them if they want to nominate someone to be a member of an *ad hoc* task force to work on our response. Therefore if this sort of work interests you at all – and you have something to say (!) – you should let the Society know.

And finally, are you a postdoc or graduate student looking for a job? If you are, you should find a new page on our web site helpful. This page provides links with very many of the sites that you might want to look at for job advertisements. If you think that there are important links missing please inform Emma Southern, Head of Communications (esouthern.bsf@physoc.org).

Richard Dyer
Chief Executive Officer

Biosciences Federation Careers Conferences 2006
University of Reading
Saturday 2 December

For undergraduates, graduates, postgraduates and postdocs from all branches of life science

£12, including refreshments and lunch

For full details of the programme and a booking form, please visit
http://www.bsf.ac.uk/careers/careersconf.htm

Long and tortuous goodbye to Stud Muffin No 1

Cats and Rentokil have it easy. Biomedical researchers, however, suffer greatly when they have to kill mice in the lab.

As a biomedical researcher I am afflicted with a serious problem. It's a transgenic mouse that has been engineered with the ability to wreck my career. I would like to kill it, but the multiple sheets of paper I would have to fill in, the computer records I would need to input and the bizarre procedures I would be required to follow might take me several hours. I just don't have the time. This devious creature has entered into a conspiracy with the British state, and it has nearly as many rights as me.

In the past 5 years there has been an explosion of nit-picking legislation intended to provide a paper trail so that some faceless bureaucrat can microscopically follow every stage of every transgenic mouse's life.

No area of transgenic mouse life is sacrosanct. Even if I place a male mouse with a female mouse 'to do what comes naturally', it is now a procedure and needs to be recorded first, both on paper (3 sheets of) and on the computer. Imagine trying that in your own bedroom.

This bureaucracy wastes time and taxpayers' money, creates paranoia and can result in a sinister kind of predatory wildlife called a Home Office inspector hanging around your workplace.

Nobody appears to be able to stand up to this regulatory excess. I suspect that by making animal experimentation as long-winded and tortuous as possible, the hope is to make it difficult to do any real work.

The day I see a mouse pay National Insurance contributions I might delude myself that it is a sentient creature. But it is not. No research has ever demonstrated that rodents think and experience suffering in a manner that even closely resembles the human condition. People who convince themselves otherwise generally have something missing from their lives – worrying about the non-existent consciousness of mice is probably the nearest thing to a meaningful relationship that they have.

The bottom line is that mice are vermin. Nobody really cares what happens to them – even the 'vegan' cat living with the animal rights nutcase down the road eats 200 a year. They make small, furry and delicious entrées for every predator on the planet.

In one study, Britain's domestic cats were thought to account for more than 300 million a year. I am surprised the Home Office hasn't tried to regulate that – it's an opportunity to collect an extra 900 million sheets of paper and they could prosecute the odd moggy for filling out the forms wrong.

If you switched on the kitchen light at 2 a.m. and found one scurrying across the floor, you would simply call Rentokil to administer an exotic-flavoured warfarin overdose. But if the mouse is a cute white colour, doesn't steal your cornflakes, is used to find cures for human diseases and lives in a university, then any attempt to kill it involves so much time-wasting drivel.

Mice attract two types of unsavoury creatures to your laboratory – animal rights lunatics and the far more fanatically unbalanced Home Office inspector. The former simply has a balanced aura and an infantile ideology to maintain. The latter is a humourless bureaucratic equivalent of Hezbollah with a £60,000 salary and a mortgage to defend. Whenever a Home Office inspector turns up, everything in the workplace grinds to a halt. Experiments get cancelled and all sorts of lunacy occurs.

In the last place I worked, a researcher was reprimanded for using secret codes on a cage label. Her crime was to write the symbol ®. This Masonic symbol stood for Rachel. Another was admonished for calling a mouse 'Stud Muffin No 1' (he produced lots of kids). The Home Office inspector was appalled, though it may have done wonders for the mouse's ego.

Still, there is hope. Someone has devised a way of inserting a luminescent gene into mice. They are a genius. If I had my way, the gene would be inserted into every mouse on the planet so that the next time you walked into the kitchen at 2 a.m. you wouldn't need to switch on the light. The mice could just be sitting there in the moonlight innocently fluorescing at each other. And that would make them far easier to kill.

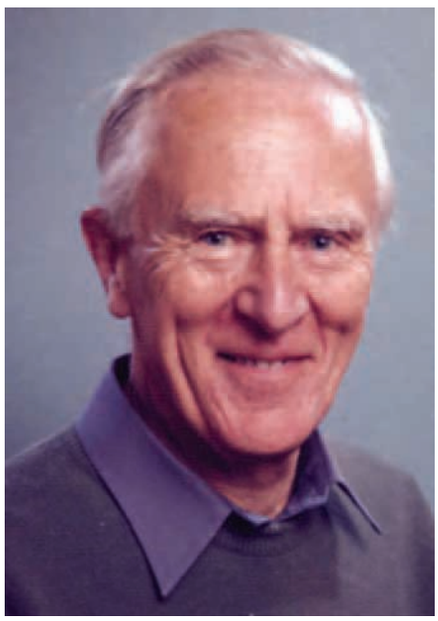
The author would like to remain anonymous. The last time he killed a mouse in his kitchen he used a £2 trap from B&Q. When he killed a mouse at university he filled in three sheets of paper and one Excel file, and needed a training certificate, a named day-to-day care officer and a special white suit.

Keith Cormorant

This article first appeared in The Times Higher Education Supplement (http://www.thes.co.uk) *on 22 September 2006, and is reprinted here with permission.*

Douglas L Ingram

1929–2006



The death of Doug Ingram from cancer at his home in Whittlesford, Cambridge on 21 March marks the end of a unique scientist and human being. He had a tremendous love of science and lived life to the full. His research career spanned four decades during which time he made major contributions to the fields of reproductive physiology, thermal and environmental physiology, and nutritional and developmental physiology. Not only did his findings result in significant insight into fundamental biology but they also paved the way for current applications in biomedicine. He was extremely modest about his ability and achievements, frequently attributing major advances to his colleagues. Despite being a full-time research scientist, Doug also made time to help others – his knowledge and enthusiasm for science have been passed on to numerous students and colleagues world-wide.

The major part of Doug's research achievement occurred between 1961 and 1989 at the ARC Institute of Animal Physiology, Cambridge/BBSRC Babraham Institute, in the Departments of Applied Biology, Cell Biology, and Molecular and Cellular Physiology. He was a Member of The Physiological Society from 1963 to 2001. Doug was Visiting Lecturer and Research Fellow, Departments of Veterinary and Medical Physiology, University of California at Davis, USA (1968–1969), Lecturer in Climatic Physiology, Department of Biological Anthropology, University of Cambridge (1974–1997), Special Professor of Environmental Physiology, University of Nottingham (1981–1989), and Supervisor in Physiology (1969–1999) for undergraduates in Medical, Veterinary and Natural Sciences at Gonville and Caius College, Newnham College, Churchill College and Christ's College, University of Cambridge. He was a Member of the High Table at Christ's until March 2006.

Doug was always passionate about biology. He was born and brought up in Birmingham where the parks and small rivers provided early opportunities for discoveries about the natural environment. He shared with his father, a shoe-repairer, the intellectual curiosity and practical ability that are essential for success as a first-rate research scientist. Enlightened post-war policies on further education for those with academic ability but limited financial resources, together with a City of Birmingham Exhibition, enabled him to join his local university during a period of immense research achievement and leadership. He was an undergraduate in the Department of Zoology under Peter Medawar and then a PhD student in the Department of Anatomy under Solly Zuckerman. His studies on reproductive physiology were interrupted by a 2 year period of National Service as a Royal Air Force Education Officer, after which time he was awarded a 3 year MRC Research Fellowship to return to the University of Birmingham under Zuckerman. His work was concerned with the problem of atresia which causes a decline in the number of oocytes in the mammalian ovary. It provides the impetus for many current studies on germline stem cells and follicular renewal in the postnatal mammalian ovary; studies that have significant clinical implications with respect to ovarian failure.

Key aspects of environmental physiology, especially thermoregulation and adaptation to the thermal environment, formed the basis for the major phase of Doug's research career, first at the ARC Hannah Research Institute (1958–1961) and then at The Babraham Institute, Cambridge. He carried out many detailed investigations, often with co-workers, into the role of thermosensitive regions deep in the body and on the skin surface. His research was concerned with both behavioural and autonomic systems, such as blood flow and metabolism, and it was concluded that the control systems depend on the integration of signals from all over the body. At this stage he also initiated studies into interactions between nutrition and the thermal environment. The effects of changes in environmental conditions were investigated in relation to a range of variables such as sensible and evaporative heat loss and the quantity of food eaten, and demonstrated a striking interaction between behavioural thermoregulation and food intake.

These studies resulted in numerous publications in learned journals, including *The Journal of Physiology*, and joint publication of the definitive book on *Man and animals in hot environments*. This work continues to provide insight into fundamental mechanisms of thermoregulation. In the current environment of global climate change his contribution is particularly relevant to an understanding of the potential for homeostatic adaptation in all mammalian species. In recognition of his achievements, he was awarded Individual Merit Promotion to Senior Principal Scientific Officer in 1975, and a DSc by the University of Birmingham and elected a Fellow of the Institute of Biology in 1976.

The last 15 years of Doug's research career saw a remarkable period of scientific achievement. He did not seek high office but chose to continue in practical research, during which time he demonstrated unique ability as an integrative scientist. This research, with many colleagues, visiting scientists and students, highlighted his continuing flair for asking the right questions and the ability to answer them by developing new techniques. Of particular importance are studies on the influence of environmental temperature and energy intake on postnatal

development. Some environmentally and nutritionally induced changes were found to be at least as great as those determined by genetics and the underlying mechanisms involved physiological, biochemical, cellular and molecular modifications. His studies highlighted the role of the endocrine system, especially thyroid and growth hormones, in these responses. For example, it was found that temperature and energy intake influence thyroid hormone metabolism through separate mechanisms, and that the abundance of nuclear thyroid hormone receptors is determined by an interaction between thermal and nutritional factors. This research provided new insight into fundamental problems of growth and development and has led to increased understanding of the mechanisms by which early environment has both immediate and long-term effects on health and disease. When Doug retired from The Babraham Institute, the Director wrote about his impressive productivity and pioneering research since Individual Merit Promotion, and said 'As the march of science has been taking an ever more molecular path, it has been reassuring for me to know that some of our staff have continued a whole animal approach. In this regard I have always found your work both exciting and comprehensible. Especially revealing to my mind is the extraordinary phenotypic change brought about by ambient temperature differentials, surely a timely leveller for the almighty gene.'

Following formal retirement, Doug continued to demonstrate his love of science and desire to seek answers to the deeper questions about life. In addition to teaching undergraduates, he read widely and studied astronomy and cosmology at the Institute of Continuing Education, University of Cambridge. In his final year he showed tremendous courage in the face of deteriorating health. He continued to pursue his interests in philosophy, baroque music, sailing and walking, and enjoyed intellectual discussions with former colleagues and friends. A testimonial in 1955 stated 'He is a man of high intelligence, bright disposition of ideas and practical ability. His moral character is of the highest standard'. Numerous letters of condolence to his family provide continuing testimony: 'a truly good and kind man', 'I remember him with great affection as a boss who actually cared about those under his charge – he was tolerant, understanding and inspirational', 'a wonderful colleague and I always appreciated his advice and help on numerous occasions', 'we all liked Doug so much, and his quiet modesty belied his considerable achievements and international reputation in the scientific field.' Perhaps most of all Doug was a person of wonderful humanity and sense of fun. He is greatly missed and will not be forgotten; his legacy lives on through the wisdom and kindness he gave to his family, colleagues and friends.

Joy Dauncey
Fellow of Wolfson College, University of Cambridge

MOLECULAR TECHNIQUES FOR LIFE SCIENCES
PCR Theory and Practice

22–26 January 2007
A five day course to introduce participants to this core technique covering the basics to quantitative Real-time PCR. Cost: £870 (Standard), £740 (CPD Accredited). For further information and application form visit www.caledonian.ac.uk/mtls

IUPS

Kyoto, Japan (27 July–1 August 2009) http://www.iups.org

IMAGES OF BRAZIL

Photos from the sessions at the Joint International Meeting with the Brazilian Physiological Society will be published in PN 66

(*photos by Prem Kumar and Nana Voitenko*)