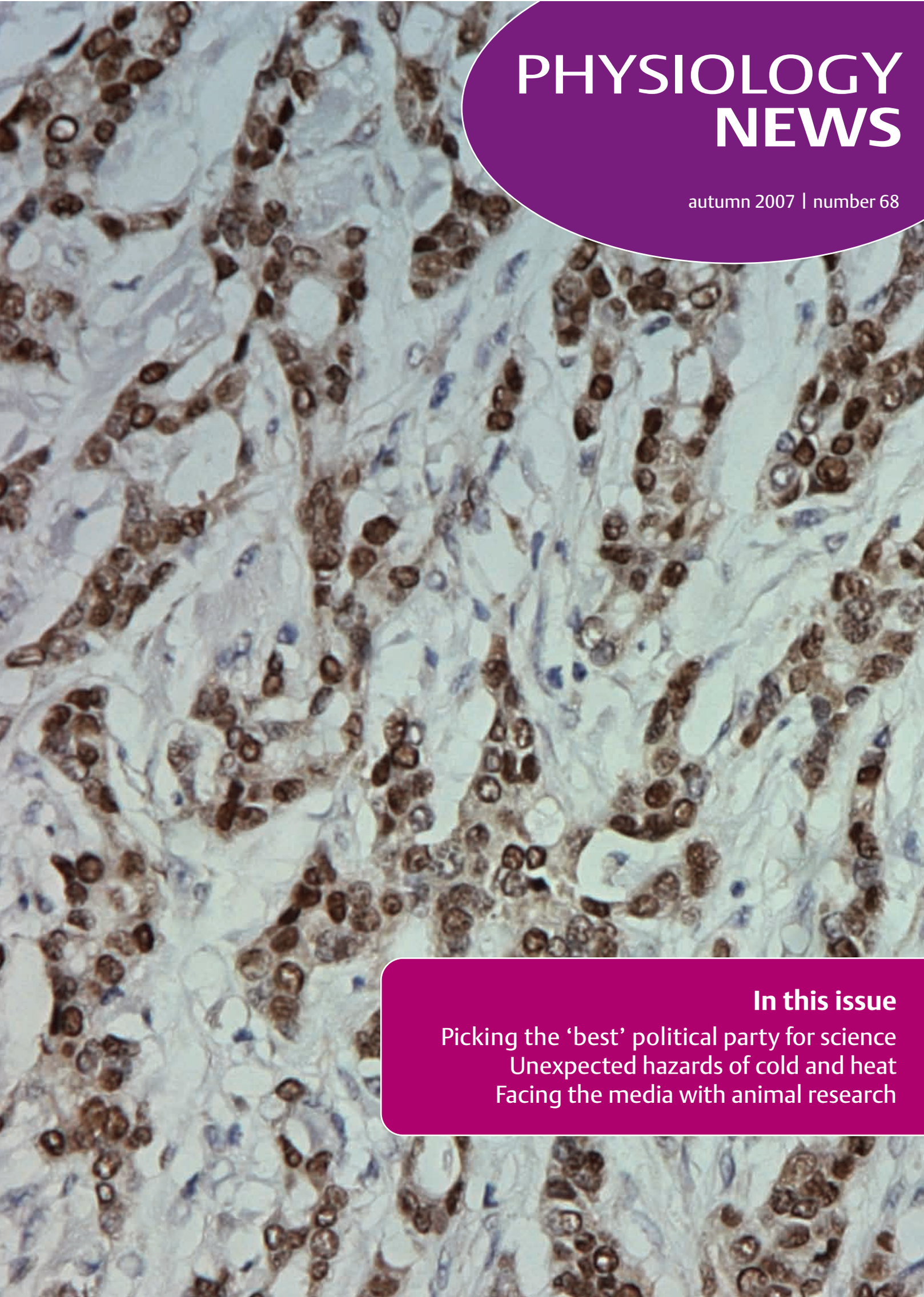
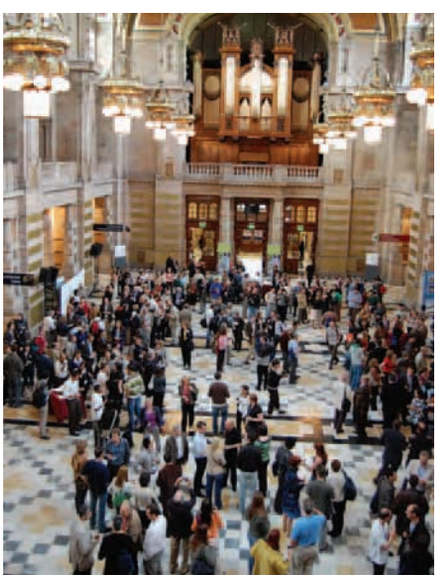


PHYSIOLOGY NEWS

autumn 2007 | number 68

In this issue

LifeSciences2007
8–12 July 2007, Glasgow, UK



Photos by Nick Boros - Toby and Ivor Williams

A full report and more images of LifeSciences2007 will appear in the next issue of *Physiology News*.

PHYSIOLOGY NEWS

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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Contributions and queries
Senior Publications Executive
Linda Rimmer
The Physiological Society Publications Office
P O Box 502, Cambridge CB1 0AL, UK

Tel: +44 (0)1223 400180
Fax: +44 (0)1223 246858
Email: lrimmer@physoc.org
Web site: http://www.physoc.org

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PHYSIOLOGY NEWS

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Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Winter 2007 issue, No. 69, should reach the Publications Office (lrimmer@physoc.org) by **12 October 2007**. 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 Senior Publications Executive or a member of the Editorial Board of *Physiology News* (see contents page for details).

Physiology News Online
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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 Senior Publications Executive.

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* at http://www.physoc.org).

Opinions expressed in articles and letters submitted by, or commissioned from, Members, Affiliates or outside bodies are not necessarily those of The Physiological Society.

In this issue

Welcome to the Autumn 2007 *Physiology News*.

Recent ministerial changes and departmental restructurings in the UK have 'moved' governmental responsibility for science and science policy. It is therefore appropriate that this issue sees our first editorial from outside The Society, as Hilary Leevers from CASE discusses the attitude of the UK political parties to science. There are some positives, although the demise of the House of Commons Select Committee on Science and Technology is a worrying development, as testified by open letters from the scientific community in the press pleading for its retention, e.g.
http://education.guardian.co.uk/higher/news/story/0,,2130978,00.html

This issue also sees our first diary from the private sector (p. 12), and a look at the improving climate for animal research (p. 37–39). We also have all our regular features.

Exercise features large in the News and Views articles (four in my count), as well as appearing in *Teachers turn students for the day* (p. 43), in *From the archives* (p. 45), and in the book reviews (p. 55). Given the increasing concern about obesity in the UK's population, including children, and in our pets too if you believe recent news reports, perhaps this will prompt more sedentary physiologists (including me!) to get exercising.

Austin Elliott
Editor

A week in the life of ...
David Bunton (p. 12)

Picking the 'best' political party for science

The recent reorganisation of Government ministries gives some indication of what the new Prime Minister thinks of science. He has spent most of the last 10 years telling us that science and technology are crucial to the country's future, but despite expectant rumours to the contrary, he baulked at the idea of creating a Department of State with the word 'science' in its title.

The structure that Gordon Brown did create – a Department for Innovation, Universities and Skills – gives a very clear picture of his view of *why* science is important. He wants the people of Britain to develop science and engineering skills in order to engage in the innovation that will drive the economy. Science is a utilitarian endeavour that can be utilised to enhance social, cultural, environmental and especially economic wellbeing.

Nobody can disagree about the economic utility of science. Every aspect of the economy is based on technology in one way or another, and the UK will certainly become a much poorer country if we do not put our research to good use. But a good deal of Labour's effort over the past few years has seemed to work from the assumption that by forcing the research community into doing research with predicted 'economic impact,' they can create a prosperous high-technology sector. In fact, the universities have changed out of all recognition over the last decade and a half, and it seems that almost every young researcher wants to spin out a company or license his or her technology. More effort should now be going into creating the economic conditions in which industry is willing and able to pull those technologies through.

But the one thing you cannot take away from the Labour Party is the dramatic increase in the total finance available for research, so that we can now discuss what to do with the money rather than complaining because there isn't any.

Tony Blair promised 'education, education and education' and Gordon Brown wants the UK to be 'the most educated nation in the world' but their policies so far have failed to tackle the country's real educational problems, certainly in science. A million children are taught physics by unqualified teachers, three quarters of schools are cancelling practical classes, and universities lose money on every science student they take.

Ian Pearson, the new science minister has said: 'I express a personal oath that science will run through, and be at the heart of, the new Department's policies. [You] will not find us lacking in making sure that science is regarded as being of the utmost importance.' These are fine words, and everyone in the science community will hope they are fulfilled. Hopefully, Pearson will not let other ministers raid the science budget of £98 million, as his predecessor did in February, with a rather casual attitude to the so-called 'ring fence' that is meant to protect it.

Until about 2005, the Conservative Party spent years ignoring the existence of science policy, let alone engaging with the science community. But in the last couple of years, all of that has changed. Shadow Chancellor George Osborne has used his platform to criticise the lack of academic freedom inherent in some of Gordon Brown's policies. But his plans for a 'flatter' tax regime, while plausible and attractive in principle could harm science unless they were implemented with safeguards to protect the benefits currently delivered by the tax credits available for research and development, especially those that support smaller companies.

The Opposition education team has started getting to grips with the big issues – like the dramatic shortage of qualified teachers and the need to fund really interesting research. Boris Johnson's work at Higher Education and David Willetts' interest across the range of educational issues have started to develop some interesting thinking about science. Mr Willetts will be giving CaSE's Annual Distinguished Lecture on 17 October and setting out some more detail (details from Susan O'Dwyer on 020 7670 4995). Iain Duncan Smith's review of social breakdown has also identified the need to address poor educational achievement in some communities, especially in hard subjects like science.

Importantly, David Cameron's overall review of his Party's policies includes a taskforce under former Science Minister Ian Taylor that is looking into all aspects of science and technology. Most interestingly, the group has recognised the need to fund genuinely novel research of the kind that is getting squeezed out by the increasing bureaucracy and central control associated with most Government funding. Taylor has proposed an Innovative Projects Agency (IPA) with a budget of £1 billion a year to 'create a bridge that links the ideas of today to the industries and products of tomorrow'. Crucially, the IPA is intended to be tolerant of risk. 'Put simply,' says Ian Taylor, 'the Research Councils support research; the IPA would procure development'. The organisation will be free from intrusive intervention from Ministers and civil servants, and the taskforce has recognised that it will need a special arrangement with the National Audit Office, which has a risk-averse attitude that can be harmful to research.

Not surprisingly, it's harder to define a specific science agenda from the third party Liberal Democrats, but a number of their key players are driving important agendas. Phil Willis, who took the Chair of the House of Commons Science & Technology Committee after the last election, has made great efforts to emphasise that the more he learns about science policy, the more clearly he understands how everything is interrelated. We need far more coordination of scientific policies than has been the case under all Governments for the past 20 years. His colleague Evan Harris has been a great friend to the scientific community – especially physiology researchers – as an outspoken defender of animal research, while in the House of Lords, Margaret Sharp has been relentless in holding the Government to account on its Higher Education policy. In a recent debate, she posed hard questions about how we can adequately fund research across a diverse university system, making sure that the high flying institutions can complete on a global stage without condemning the students in other universities to courses that do not involve proper honours-level research projects.

If you had to pick a political Party that was 'best' for science, it would not necessarily be easy. But in all of the major groups these days, there is at least an understanding that science policy cannot be ignored in the way that it used to be. That is a great opportunity for the science community, and we should make sure we use it.

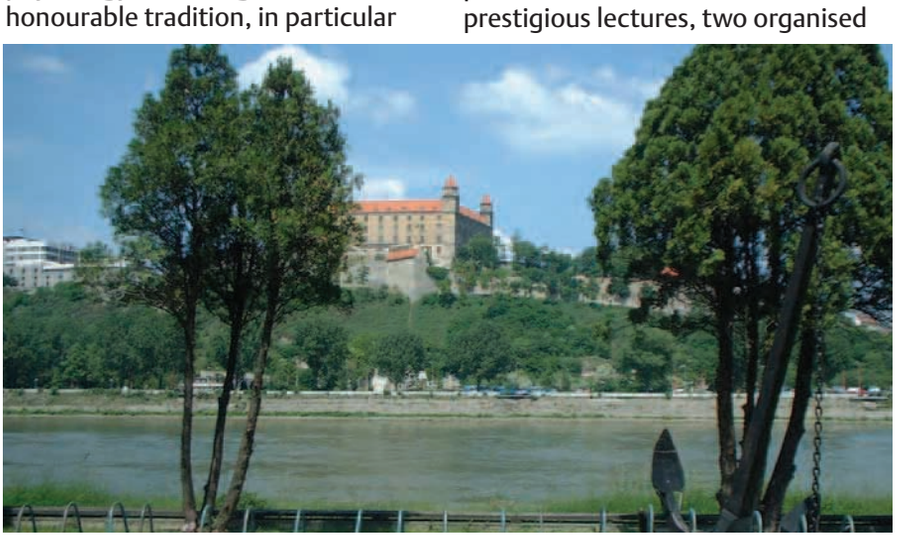
Hilary Leevers
Acting Director, Campaign for Science & Engineering, London, UK

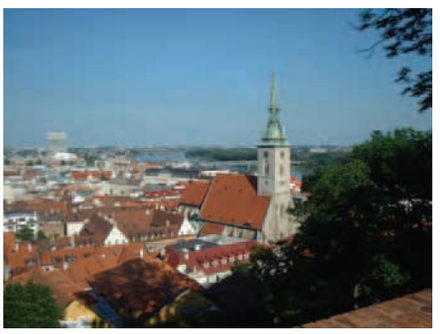
Physiological sciences meet up in Bratislava

This September sees three physiological societies (the Slovak Society, FEPS and our own Society) joining up to host a meeting in Bratislava, the capital of Slovakia. The idea for such a joint venture originated after a FEPS committee meeting in 2003 that saw the inclusion of several physiological societies from Eastern European countries into the wider fold of European physiology. There was, and still is, clearly a desire for physiologists in many such countries to become more involved internationally. However, a number of factors, not least the cost of travel, limited for many the ability to participate freely. It was thought that a general physiological societies' meeting in central Europe would faciliate better exchange among scientists throughout Europe and so the motivation for this meeting was born.

Bratislava was an excellent choice for many reasons: it is centrally located with good connections; it is relatively inexpensive, at least compared to most of western Europe, and Slovak physiology has a long and honourable tradition, in particular after the formal establishment of the Slovak Academy of Sciences in 1953. There remains also a close link with the Czech society, exemplified by the annual Physiological Days meeting. An example of how Slovak science has impacted on public health comes from the Institute of Experimental Endocrinology, of which our host Vladimir Strbak is currently Director. Goitre was endemic in Slovakia and one of the first projects of the Institute after its foundation in 1951 was to find its cause and implement a programme of iodine prophylaxis by salt iodination, one which achieved resounding success.

The meeting will host 15 widely differing symposia on the mornings of each day, and will incorporate free communications from submitted abstracts. The afternoon sessions will be devoted to other oral and poster sessions. There are also three prestigious lectures, two organised by FEPS and our Society given by Torben Clausen and Ian McGrath, as well as an IUPS lecture given by Ole Petersen. Preceding this is a European Young Physiologists day that allows the new generation of physiologists to choose the agenda and provide pointers for the future.





Outside the meeting, Bratislava is a charming place with an old city dominated by the Danube, and overlooked by a castle that offers fantastic views of the city. You can travel along the Danube by boat to Vienna or even to Budapest if you want a longer excursion, walk into Austria or Hungary themselves along the Danube – they are only a few kilometres away! - or go immediately to the north to the origins of the Carpathian mountains, from where they arc round central Europe for 1500 km back to the Danube in Romania. For those interested in the less obvious sights, to the south of the river is a truly gigantic panelák, the huge and uniform blocks of flats erected by Communist governments as a monument to collectivism and a desire for affordable housing, connected to the old town by a striking bridge.

Whatever your reason for attending, all the organisers welcome you to Bratislava and trust you will find the meeting valuable and fun.

Chris Fry

Physiology in Galicia

Alexej Verkhratsky sets the scene for The Society's International Workshop

This year The Physiological Society will explore the depths of Western Ukraine. The workshop on *Molecular physiology of membrane transport and cell excitability* (organised by Alexei Verkhratsky, Oleg Krishtal, Andrey Sibirny and Volodymir Lushchak) will take place in the Carpathian Mountains, in the small resort of Yaremche. Various aspects of molecular physiology of membrane transport will be presented by invited lecturers (see box below), and 40 students will be given the opportunity to present both oral and poster presentations. This meeting continues the very successful series of Society workshops, which have run throughout Europe, from Seville to Prague, Bucharest, Krakow and Kiev to St Petersburg. Incidentally, the very first Society workshop was organised in Ukraine in Kiev in 2000, and more than 500 students and 100 invited lecturers have participated in the workshops since then.

Western Ukraine has a long and turbulent history. It was the only Kievan Rus Princedom which withstood the Tatar invasion in the 13th century, remaining independent as Halych-Volyn Principality well into the 14th century. Then it gradually fell under Polish control, and in 1569 became a part of the Polish-Lithuanian-Ukrainian Commonwealth (or 'Rech Pospolitaya'). This was a most unusual European political system, based on a democracy of gentry, which elected kings and declared wars under consensus principles: every nobleman – and these nobleman or 'shlyachta' numbered around 500,000 – had a *liberum veto* [the forbidding voice], and by casting the *veto* every gentleman could block any and all decision(s). Amazingly, this system worked for many generations and, in the 16th and 17th century Polish-Lithuanian Commonwealth, to a large extent shaped the history of Eastern Europe. At the beginning of the17th century, Polish-Ukrainian troops occupied Moscow and remained until 1618.

Yet the country was internally unstable and plagued with both nationalistic and religious differences. These resulted in the 1648 Great Civil War in which millions of Ukrainians and Poles perished, thus eventually ruining the Commonwealth. This period of decline was heroically interrupted in 1683, when the Polish-Ukrainian army, led by Jan Sobiessky, routed the Turks under the walls of Vienna, saving the South-East of Europe from devastation. The 18th century witnessed the further decay of the Polish-Lithuanian Commonwealth, until finally between 1772 and 1795 all its lands were partitioned between Russia, Austria and Prussia; Galicia was delivered into the hands of the Austrian emperor and remained a part of the Austro-Hungarian Empire until the end of World War I.

The Treaty of Versailles in 1919 dismantled Austro-Hungary, and Galicia became part of the recreated Poland until 1939, when, under the framework of the Molotov-Ribbentrop Nazi-Soviet pact, it was invaded by Soviet troops. During World War II the Ukraine was a major battleground of the Eastern Front, seeing vicious fighting and savage guerilla war. Great tragedies befell the region, with the death and displacement of a large proportion of its inhabitants, including the systematic murder of much of Ukraine's Jewish population. The total WWII civilian death roll in the Ukraine has been estimated at 5–8 million. Galicia was successively occupied by Soviet, German and again in 1944 by

Clockwise from above: Yaremche; the monastery in the Karpathian mountains; the mountain river.

Invited speakers

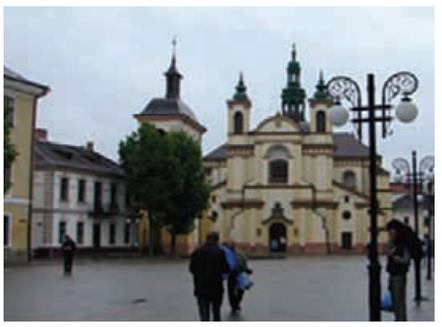
Alexandr Chvatal (*Prague , Czech Republic*)
Graham McGeown (*Belfast, UK*)
Jerzi Duszynski (*Warsaw, Poland*)
Francis Edwards (*London, UK*)
Leshek Kachmarek (*Warsaw, Poland*)
Oleg Krishtal (*Kiev, Ukraine*)
Volodymyr Lushchak (*Ivano-Frankovsk, Ukraine*)
Erwin Neher (*Göttingen, Germany*)
Alan North (*Manchester, UK*)
Ole Petersen (*Liverpool, UK*)
Bert Sakmann (*Heidelberg, Germany*)
Andras Spät (*Budapest, Hungary*)

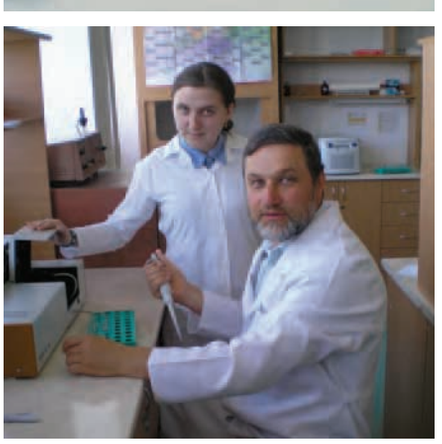
Soviet forces, with this final occupation forcibly re-incorporating Western Ukraine into the Soviet Union. The modern history of the Ukraine began on 24 August 1991, when Independence was declared following the collapse of Soviet communism.

Galicia has long-lasting academic traditions. The first academic institution was established in 1586 as a form of the 'Brotherhood School', which taught languages, mathematics, astronomy, philosophy and rhetoric. The first university (which initially was almost entirely dedicated to theology and philosophy and was controlled by Jesuits) was opened in Lviv on 20 January 1661. In the 18th century chairs in mathematics, physics and astronomy were established. This Jesuit university was closed in 1773, after the dismantling of the Jesuit order.

In 1784, however, EmperorJoseph II decreed the creation of a new University of Lviv, which was officially opened on 16 November 1784. The University comprised four faculties (philosophy, law, medicine and theology) and the appointment procedure (at least on paper) was decreed to be open and based on merit – the nationality and religion of prospective candidates being irrelevant.

Physiology was taught in Lviv from 1895, when Adolf Beck (1863–1942) accepted a chair in animal physiology. Beck was a remarkable neurophysiologist, and remains the most famous physiologist to work in Lviv. His research was mainly dedicated to electroencephalography. He was one of the first to discover the spontaneous cerebral potential oscillations (these observations were published in 1890 in *Centerblatt für Physiologie*). Incidentally, the same spontaneous electrical activity was observed by Richard Caton in Liverpool in 1875. Adolf Beck also described the localization of sensory modalities on the cerebral cortex by electrical or sensory stimulation and by recording electrical activities with clay electrodes and a string galvanometer. Using these techniques Beck also discovered a potential decrease in sensory stimulation. Further advances in physiology in Lviv University were also closely connected with the Polish physiologists Jakub Kostzhevski, Tomash Sadej and Gustav Piottovski. At present the Department of Physiology is mainly concentrating on the investigations of electrophysiology and calcium signalling in various types of secretory cells.





The 2007 Society workshop will be hosted by two Galician institutions, the Institute of Cell Biology (ICB) based in Lviv and the Department of Biochemistry at Precarpathian University. The ICB, under the directorship of Andrey Sibirny, was established in 2000 as a research institute of the Ukrainian Academy of Sciences. The Institute has four research departments and two laboratories, which employs ~100 staff, working in various aspects of cell and molecular biology, microbiology, biochemistry, genetics and immunology and biotechnology.

The Department of Biochemistry, headed by Volodymyr Lushchack, was created in 2002 in the new Precarpathian National University, named after the Ukrainian writer Vassyl Stefanyk, granted university status in 1993. The Department has six academics, nine technicians and 10 PhD students, focusing on the investigation of free radical metabolism in bacteria, yeast and fish.

The workshop will be held in the recreation complex ('Karpaty'), which is located in the picturesque resort city of Yaremche about 60 km from Ivano-Frankivsk at an altitude of 650 m above sea level. The city of Yaremche was founded at the end of 18th century. The city's nickname is 'Pearl of the Carpathians', which reflects its unique beauty. Yaremche is surrounded by wooded, picturesque mountains. The Prut River flows through the area and falls through a scenic gorge that is visited by many tourists.

Nataliya Fedirko
University of Lviv, Ukraine
Alexej Verkhratsky
University of Manchester, UK

From top: Central square, Ivano-Frankivsk; old Town Hall, Ivano-Frankivsk; main building of the University of Lviv; wooden Ukrainian church in the Carpathian mountains; Volodymyr Lushchak in his laboratory.

Why did the amino acid cross the placenta? ... to get to the other side

Jane Cleal (pictured right) presents the work which won her the Blue Riband Prize at the recent Society Focused Meeting in Edinburgh

I am a postdoctoral research fellow working with Rohan Lewis and Mark Hanson at the Institute of Developmental Sciences at the University of Southampton. After completing a PhD in 2005 which studied the long term physiological effects of altered fetal and infant nutrient supply using *in vivo* whole systems physiology, I worked for a year on a commercially funded project developing a new fetal ECG monitor before taking up my current position last year.

The placenta is a fascinating organ which acts as an interface between the mother and the fetus. One of the major roles of the placenta is to supply the fetus with nutrients. If the placenta cannot do this the fetus will become growth restricted and is more likely to become ill or die after birth. Furthermore, fetuses who do not grow properly *in utero* are at greater risk of chronic disease in adult life (Gluckman & Hanson, 2004). I am particularly interested in the transport of amino acids across the placenta. As well as forming the building blocks of proteins, amino acids are required as metabolic precursors for multiple essential biosynthetic pathways and for fetal energy metabolism. Impaired amino acid transport is associated with intrauterine growth restriction (Jansson *et al.* 2006) and understanding the processes involved in placental amino acid transport is crucial.

Transport of amino acids from the mother to the fetus involves amino acid uptake by the maternal facing microvillous membrane (MVM) and efflux across the fetal facing basal membrane (BM) of the placental syncytiotrophoblast. The two main types of amino acid transporter involved in amino acid transport are Na^+ dependent transporters and amino acid exchangers (Fig. 1). The mechanisms of transport protein mediated amino acid uptake by cells are well understood and their function in the placenta has been extensively studied. In contrast, much less attention has been given to the release of amino acids from the BM of the placental syncytiotrophoblast, and this process is still not well understood, particularly as the Na^+ dependent transporters that are so important for amino acid uptake are not thought to mediate efflux and so cannot contribute directly to amino acid efflux from the BM. The current focus of my work is therefore to establish the mechanisms of amino acid transport across the BM of the placenta into the fetal circulation.

Jane Cleal and her New Forest pony, Farrier's Brown Bear, winning the British Riding Clubs' National Cross Country Championships in 2006.

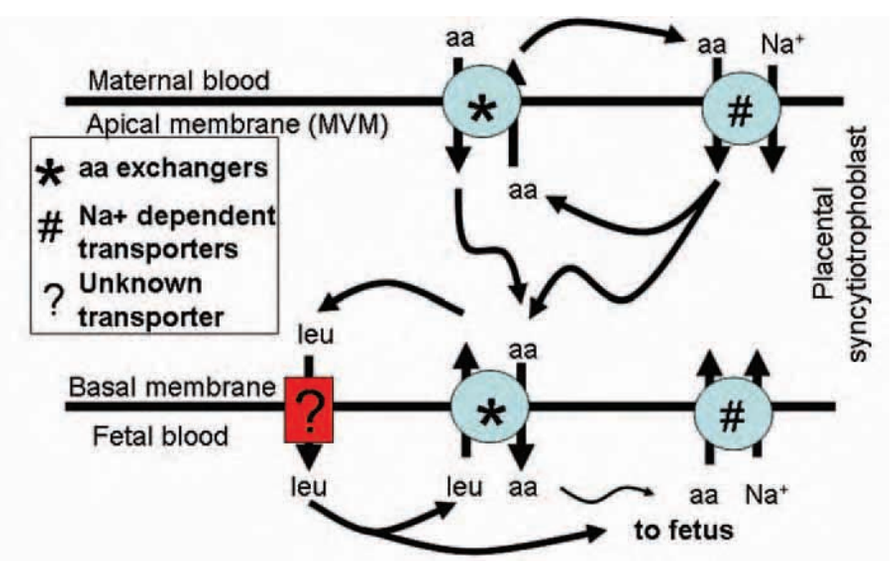


Figure 1. Amino acid (aa) transport across the placental syncytiotrophoblast. Na^+ dependent transporters (#) mediate influx but not efflux of amino acids. Transport by exchange (*) can only occur when there are amino acids present on both sides of the cell membrane. We have demonstrated that amino acid efflux acros the BM occurs by mechanisms other than exchangers; however, the transporters that mediate this have not yet been identified.

I have been using a novel adaptation of the isolated perfused human placental cotyledon technique developed in our laboratory. This allows us to study the transport of amino acids out of the placenta and into the fetal circulation in intact placental tissue. Knowing that amino acid exchangers are obligate exchangers, whereby they cannot operate unless they transport one amino acid from within the placenta in exchange for one fetal amino acid on the fetal side of the BM (Fig. 1), has allowed us to study their activity

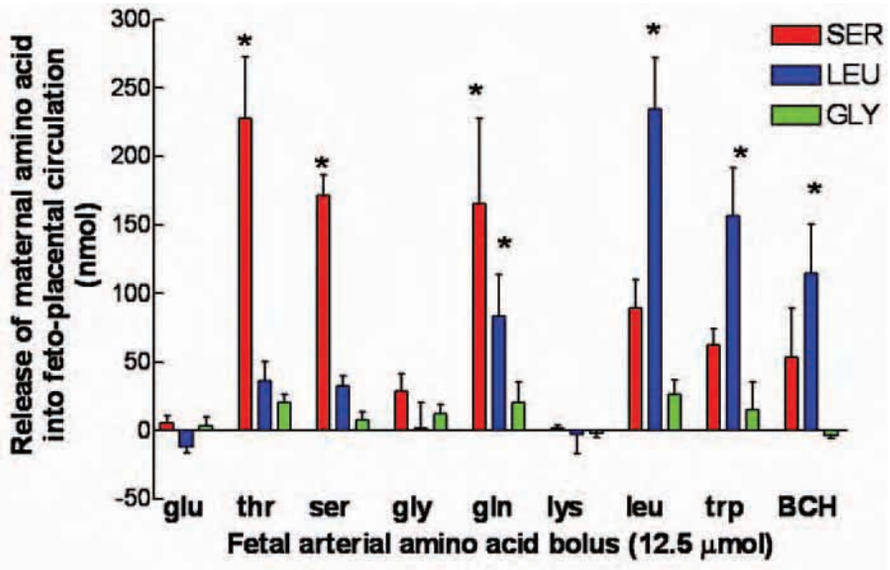


Figure 2. Serine, leucine and glycine release into the fetal circulation following fetal amino acid boli: data (mean ± SEM) is presented as AUC. * $P < 0.05$ the AUC is different from glutamate (Cleal *et al*. 2007).

on the BM by altering the concentrations of amino acids in the fetal circulation. Adding specific amino acids that are substrates of specific exchangers to the fetal circulation will activate that exchanger and allow us to observe its activity. In this way we are characterizing the activity of amino acid exchange on the BM of placental syncytiotrophoblast. So far we have established the fetal amino acids that stimulate exchange for serine, leucine and glycine within the placenta (Fig. 2).

However, transport by exchange is not sufficient to meet fetal amino acid requirements as one amino acid is swapped for another meaning that the number of amino acids in the fetal circulation does not increase. There must therefore be other transporters on the BM that mediate amino acid efflux. My studies have indeed identified that there is efflux of leucine, but not serine or glycine from the placenta to the fetus by means other than exchange (Fig. 3). This suggests that there are mechanisms that allow specific amino acids to be transported out of the placenta and into the fetus, and characterizing these transport systems is now the focus of my work. Once these systems have been properly characterized I plan to investigate their role in the pathogenesis of intrauterine growth retardation.

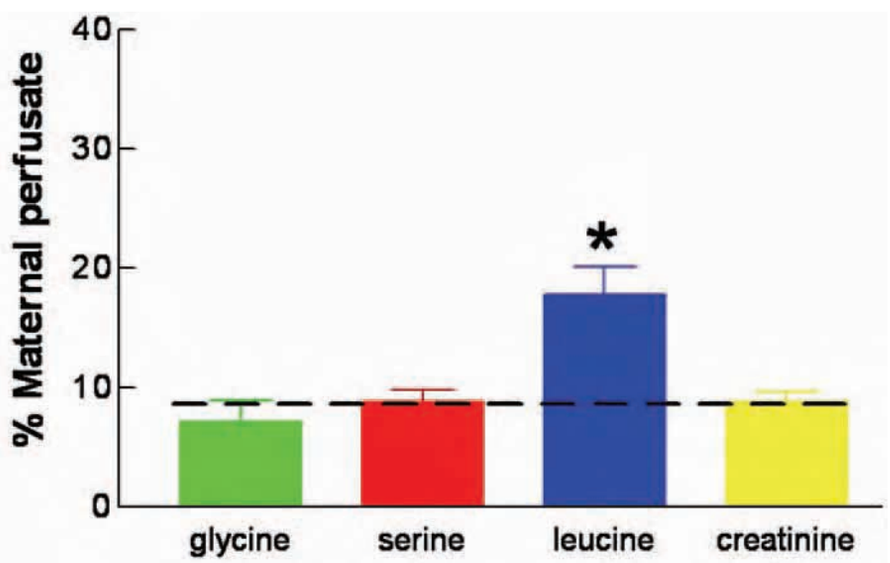


Figure 3. Fetal uptake of serine, leucine and glycine in the absence of fetal amino acids for exchange. Data (mean ± SEM) as a percentage of substrate perfused into the maternal circulation. * $P < 0.01$, different to creatinine (a marker of paracellular diffusion): below line (----) = diffusion; above line = active transport (Cleal *et al*. 2007).

Acknowledgements
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Jane Cleal
Institute of Developmental Sciences, Southampton General Hospital, Southampton, UK

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In brief

Animals in research: make up your own mind
The Society has produced a new DVD in parternship with the Coalition for Medical Progress, GlaxoSmithKline and the Biomedical Research Education Trust. The DVD was distributed to all UK schools in May 2007. To request a copy please contact Liz Bell (ebell@physoc.org).

Facing the media with animal research/The dawn of glasnost for research using animals?
Sarah Bailey, Thelma Lovick and Selina Pearson think the climate is changing – see their articles starting on p. 37.

The Royal College of Nursing
conference and events programme for 2007/2008 now available at www.rcn.org.uk.

Researching unexpected hazards of cold and heat

Cold and heat are large environmental causes of death. The nature of the hazards they present often differs greatly from general assumptions. Here William Keatinge (pictured below) describes research that showed this. Much of the research was made possible by the traditional independence of British universities and the flexibility of their research funding, and he makes a plea to restore it

As a young doctor, I found myself drafted into the Navy for 2 years. Hodgkin, Huxley and Katz's breakthroughs on nerve conduction had left me fired up to find how the brain worked. The Navy was not interested in how the brain worked, but it had lost around 30,000 people from cold immersion in World War 2, and it did need to know how to reduce deaths from cold. It sent me to McCance's department at Cambridge to investigate that. Responses to cold and heat were never at the heart of British physiology but the problems they caused, and shortage of people investigating them, repeatedly called me back from other topics.

Experiments with Malcolm Evans and Peter Cannon at Cambridge, and later with many people at Julius Comroe's Cardiovascular Research Institute in San Francisco and Sir George Pickering's Department of Medicine at Oxford, answered many questions on immersion deaths (Keatinge, 1969). Reflex gasping for breath, and high viscosity of water near freezing point, often prevented even good swimmers from swimming many yards in very cold water. That caused many people, particularly children, to drown trying to swim short distances from overturned boats to shore. Buoyancy aids could prevent that. Skin froze at 0.53°C, and could freeze in seawater, which stays liquid down to -1.9 °C. Ordinary non-waterproof clothing kept skin temperature several degrees above water temperature. In water cold enough to cause progressive body cooling, with or without clothing, exercise usually increased people's heat loss more than heat production. All that provided obvious practical advice for shipwreck victims.

The most intriguing finding was that although a thick layer of fat under the skin greatly reduced body heat loss in moderately cold water, even very fat people cooled rapidly in water colder than about 10 °C. Experiments on isolated blood vessels explained that. The vessels became paralysed by cold. Skin blood vessels normally shut down in the cold, to stop blood from carrying body heat to the skin, but at these extreme low temperatures they could no longer do so. As they relaxed at temperatures below 10 °C, and blood flow returned to the skin, even fat people cooled rapidly.

This presented a challenge. If some way could be found to make blood vessels resistant to cold paralysis, fat people would be able to work in cold water for extended periods without heating or special protection. That could be valuable for divers carrying out urgent rescue or salvage work.

Experiments in Oxford on isolated arteries showed that cold blocked their electrical response to noradrenaline, the neurohormone that makes them contract in life. Their smooth muscle cells were only a few microns wide and surrounded by tough connective tissue. This made microelectrode records difficult, but an Icelander in Oxford called Johann Axelsson was recording electrical activity of intestinal smooth muscle by a sucrose gap method. Unexpectedly, after some modification, this did work on smooth muscle of arteries, and showed that noradrenaline induced action potentials in the muscle, which in turn triggered contraction. Temperatures below 10°C blocked the electrical response, but artificial electrical stimulation could still cause contraction. Actomyosin in the cells could clearly contract at low temperature, and only the initial

Figure 1. Lynne Cox swimming to Russia and Inuit walrus skin boat

action of noradrenaline on the cell membrane failed.

Systematic recordings of electrical activity in arteries opened a whole new field. Jeffrey Graham, one of my former students at Oxford, joined me when I moved to the London Hospital Medical College. We recorded patterns of electrical activity that contract inner muscle of arteries to reduce leak of blood after injury, and unusual discharges that drove its rhythmical contractions during anoxia. We also recorded localised discharges in outer muscle that amplified its response to nerves.

Progress on cold paralysis resumed many years later, when Johann Axelsson, then dean of the medical school in Iceland, told me that Gudlaugur Fridthorssen had made a remarkable swim after his fishing boat overturned in water at 5.2 °C. Gudlaugur's companions disappeared within a few minutes, but he was able to swim for 5 hours to shore, 3 miles away. An immersion in our tank in London showed that he could indeed stabilise his body temperature in water at that temperature, with little clothing. His skin blood flow and heat loss stayed low, allowing his considerable fat layer to keep him warm. Blood vessels in his skin stayed contracted, probably because his work on the fishing boat had adapted them to cold.

In 1998 an experienced American cold water swimmer called Lynne Cox 'phoned me to say that she was going to try to swim from an American to a Russian island in the Bering Straits. Two weeks later she set out from Little Diomede Island, and I monitored her temperature by radiotelemetry from an Inuit walrus skin boat. A little over 2 hours later she landed on the Russian island to be greeted by a welcome party sent by Gorbachov. The swim led to opening of that frontier for visitors from both sides, in a striking easing of the Cold War. It also showed that Lynne could maintain safe body temperature for 2 hours in water at 7 °C. A fully monitored immersion in our tank in London showed that she could maintain low skin blood flow and stabilise body temperature in water at 5 °C. Colder water causes other problems, but down to 5 °C cold adapted people with enough fat could maintain body temperature without protection (Fig. 1).

Figure 2. Yakut in traditional outdoor winter clothing

Reports that 100,000 elderly people chill to death in their homes every winter caused huge media and public concern. We had shown that insidious hypothermia was responsible for unexplained errors being made by North Sea divers, and the MRC asked if I would investigate deaths from hypothermia in elderly people. I did not think hypothermia was causing the winter deaths, but said I would be happy to investigate what was causing them. Death certificates showed coronary and cerebral thrombosis as the cause of most winter deaths, with respiratory disease causing most of the rest, but it was argued that hypothermia was really responsible. That was plausible, as ordinary clinical thermometers only recorded temperatures down to 35 °C, the upper limit of hypothermia. Using low reading thermometers, we showed that hypothermia was extremely rare among people admitted to London hospitals. Experiments on volunteers showed that mild exposure to cold caused changes in the blood that would promote clotting (Keatinge *et al*. 1984). When blood vessels in the skin shut down to preserve body heat, salt and water were excreted. This prevented the displaced blood from overloading central organs of the body, but left the blood more concentrated and more prone to clot. The practical message was that heart attacks and strokes in winter were due to these adjustments to mild cold stress, not to severe cold overwhelming the body's defences. Elderly people needed to be fully warm.

Until then, getting support for these research projects often needed persistence, but if they were important and well planned, someone would finally free essential funds or overcome obstacles. The Medical Research Council was now so pressed for cash that any hostility from a committee member could prevent them funding a project. It even refused for a time to consider research outside limited areas that they had already designated for priority. That cut out the most innovative projects.

I was now dean of a faculty of basic medical science formed at Queen Mary and Westfield College from the departments of The London and Bart's, but support from a first rate team left me time to continue research. We now needed a Europe-wide survey to assess factors affecting winter mortality. There was little chance of MRC finance for that, but my luck was in, and the European Union's *Biomed 1* programme provided funds. The survey showed that people in countries with the severest winters took so much care to keep warm that they had little winter mortality. Protection from outdoor cold stress was as important as warm housing.

A Wellcome grant let us find that people in the world's coldest city, Yakutsk, wore massive fur clothing and remarkably had no excess mortality in winter (Fig. 2).

Excess winter deaths had now fallen to around 20,000 a year, and global warming shifted interest to heat. Coronary and cerebral thromboses cause many of the British deaths in heat waves, We had found that heat like cold stress caused increased concentration of the blood, in this case because people lose salt as well as water in sweat (Keatinge *et al*. 1986) . Once a meal replaces the salt they feel thirsty and drink water, but until then their blood remains concentrated. Gavin Donaldson and I analysed mortality trends that showed people were generally adjusting to hotter summers, but occasional unprecedented heat waves caused many deaths. Advice on managing heat stress was important when a severe heat wave was forecast. Air pollution by ozone caused some asthma and other ill health, but claims that it caused up to half of the deaths in heat waves faded when allowance was made for sunshine, which heats people as well as generating ozone, and for wind which cools people as well as blowing away ozone (Keatinge & Donaldson, 2006.

I was lucky. The new commercial style of management and loss of job security in British universities came too late to affect me. It now profoundly limits their traditional freedom to teach and research without fear or favour. Without that freedom, little of my and my colleagues' work would have been possible, and restoration of some of that freedom is the universities' main need today.

William R Keatinge
Queen Mary, University of London

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Left-handed or right-restrained?

Pat Merton (1920–2000), well known for his pioneering work on muscle spindles and muscle fatigue, was much influenced by Adrian's lectures when he was a medical student in Cambridge during World War II. Even 40 years after graduation, he kept referring to his undergraduate lecture notes in supervisions and lectures. If you were taught physiology by Pat, the following episode may help correct a little misconception.

One day, in the mid 1980s, Pat asked me to check on the statistics about left-handedness in biblical times, by reference to the original Hebrew text. The reason was that he was following Adrian's notes stating that the proportion of left-handed people had increased substantially from about 3% in biblical times to about 8–15% currently. After repeating this conclusion in his lectures a number of times he wished to reconsider the original evidence. I remember asking him what made him doubt it, but all I got was a grunt and a wink interpreted by me at the time as his way of implying that there is nothing to explain about doubting, even if it's Adrian's sacred word ...

Adrian's statistics were based on *The Book of Judges* 20:15 and 20:16. In the *King James Bible*, which Adrian used, 20:15 reads:

'*And the children of Benjamin were numbered at that time out of the cities twenty and six thousand men that drew sword*',

and in 20:16 we learn that:

'*Among all these people there were seven hundred chosen men left - handed; every one could sling stones at an hair breadth, and not miss*.'

In the Hebrew text the word interpreted as left-handed in the King James version was not one word but three: 'yter yad yemino' which literally translates as 'with his right hand tied'.

The Hebrew meaning is clear, and further explicitly described in *The First Book of Chronicles* 12:2, a clarity retained in the King James version of this passage:

'... *and could use both the right hand and the left in hurling stones and shooting arrows out of a bow, even of Saul's brethren of Benjamin*.'

In Hebrew it is immediately clear that the 700 chosen men from the tribe of Benjamin had been trained to be ambidextrous, and that the training involved restraining their right hands. Pat was satisfied that there was no basis for statistical comparison of the proportion of left-handed people in the 20th century with that in biblical times.

I believe that this part of the course, and associated interpretations, did not surface again in his lectures.

Virgilio L Lew
Department of Physiology, Development and Neuroscience, University of Cambridge, UK

New Fellows

Congratulations to Physiological Society Members Peter Barnes (Professor of Thoracic Medicine at the National Heart and Lung Institute and Head of Respiratory Medicine at Imperial College London) and William Harris (Head of the Department of Physiology, Development and Neuroscience at the University of Cambridge) on their election as Fellows of the Royal Society.

A week in the life of ... David Bunton, Chief Operating Officer at Biopta Ltd

David Bunton is co-founder and Operations Director at Biopta Ltd, a contract research organisation that carries out *in vitro* pharmacology research for the pharmaceutical and biotechnology industries. He has a physiology degree from the University of Glasgow and a PhD in vascular biology from Glasgow Caledonian University and then spent 8 years as a Lecturer in Physiology at Glasgow Caledonian's Department of Biological and Biomedical Sciences where he co-founded Biopta with Chris Hillier in 2002. David and Chris identified an emerging market for human tissue-based research services and began to develop their first instrument, the PM-1, which quickly became an opportunity to fully commercialise the research by the creation of a spin-out company. Since its inception Biopta has received numerous awards for innovation including a Scottish Executive SMART award, a John Logie Baird Award and a Nexxus Award for the innovative development of PM-1, a new system for the study of pressure and flow in isolated blood vessels. Biopta has also received approximately £1 million in private investment and has grown to a successful GLP-compliant test facility that focuses on the use of fresh human tissue for drug efficacy and safety studies. Biopta now employs 14 people at its laboratory at the University of Glasgow. Here, David Bunton (pictured right) describes a typical week at Biopta.

Monday

Our working week starts with a group meeting to plan our contract research activities, a task which is easier said than done because of the irregular pattern by which human tissues become available. As 90% of the work we do is on fresh human tissue, we need to be pretty flexible in our work patterns and thankfully have a team of people who don't mind working the odd night-shift (Fig. 1)! After that it's a trip to meet the bank manager to discuss the latest management accounts and financial forecasts. Our bank has been quite supportive of a business like ours which is very different from most of their customers. A couple of hours navigating balance sheets and cash flows thoroughly reinforce physiology as a great choice of career. Back in the lab it's a day for report writing and data analysis rather than lab work; we've discovered that when working with the NHS the number of operations that generate residual human tissue increases exponentially during the week, with peak deliveries of tissue at 5 p.m. on a Friday.

Figure 1. Claire Stevenson draws the short straw and dissects some human tissue in the small hours.

Tuesday

In addition to providing contract research services for drug safety and efficacy, we also develop new lab instruments and today we visit a company in Dundee that can potentially manufacture our new *in vitro* pharmacology instrument. Derek, Biopta's product design engineer, accompanies me to ask the technical questions and interpret the engineers' own language (again reinforcing physiology as a good choice of career). I'm impressed by their ability to rapidly understand the relevance of physiology and pharmacology instruments to drug research and development. After the journey back I start to prepare my reports for the monthly Board meeting, an important task as the reports are circulated to all the investors and our Board meetings can at times resemble an episode of The Apprentice (but no one has been fired as yet), so the documents need to be thought out well in advance.

Wednesday

Back in the office today to work on a European Framework 7 application with other SMEs (small and medium-sized enterprises) and academic groups. In our experience the use of human tissue generally fits into an industrial R&D programme in one of two areas: discovery biology or safety pharmacology. This means we get requests to participate in an extremely wide range of projects with some very specific tissue requirements. After that it's into the lab to assist with the dissection of some lung tissue and I then have time for a quick sales meeting before heading home.

Thursday

Catch the early flight to London which means a 4 a.m. rise; however, this is only 45 minutes earlier than normal because my 1 year old daughter has taken to rising at 4.45am. Despite tip-toeing around the house I still manage to wake her so we all have an early start. Karen, our CRO Manager, and I attend the UK Bio Entrepreneurial Awards at Lancaster House. Apparently the event has been moved here because a VVIP (which turns out to be Prince Charles) wanted to use the previous venue; however, the new setting is impressive and the event is a good opportunity to meet some clients face to face. Karen does a great 90 second pitch about Biopta (interesting approach for next Phys Soc?) but unfortunately we don't win our category. Infuriatingly the judges later inform us that we might have won had we been entered in the 'enabling biotechnology' category rather than 'drug discovery' by our development agency, but we resist the temptation to ever mention this.

Friday

My time spent away from the office has meant that a number of proposals need to be sent out urgently. Each project tends to be quite different so proposals often turn into a miniature grant application, often preceded by a rapid review of the relevant literature (who said cramming for exams was a futile exercise). Although we don't get to spend too long on any one project the plus side is that we all develop a real breadth of knowledge by becoming involved in various drug development programmes. At weekends we take turns being 'on call' for any human tissue that becomes available, which unsurprisingly creates mixed feelings as this weekend it's my turn!

Letter from the United Arab Emirates

Biomedical science research: from humble beginnings to an integral part of the undergraduate medical curriculum at the Faculty of Medicine and Health Sciences, United Arab Emirates University

The Faculty of Medicine and Health Sciences (FMHS), one of nine colleges in the United Arab Emirates University (UAEU), is located in the 'Garden City' of Al Ain, which forms part of the Abu Dhabi Emirate. The Faculty accepted its first cohort of medical students in 1986. The medical curriculum is a 6 year programme, comprising a 2 year medical sciences course, a 2 year organ systems course, which is followed by a 2 year clinical sciences course. Students then complete a 1 year internship. Currently, the FMHS accepts only Emirati nationals and typically has an annual intake of around 30-35 female and 15-20 male students. One of the benefits of a relatively small annual intake of students is that we are able to offer a variety of educational activities which would be difficult in larger faculties. Research is becoming an increasingly important aspect for career development and we pride ourselves in offering our students several opportunities for curricular and extra-curricular research. This article, written by Chris Howarth (who joined the Department of Physiology in 1998 from Leeds University), who oversees most of the undergraduate research and Michelle McLean (who joined the Department of Medical Education in 2006 from the University of KwaZulu-Natal, South Africa), discusses the development of undergraduate research in the FMHS.

Evidence-based medicine (EBM) involves integrating the appropriate current best clinical evidence with clinical expertise, to make decisions about individual patients (Sackett *et al.* 1996). '*Best available clinical evidence*' refers to studies that involve the basic sciences of medicine as well as those that relate, *inter alia*, to the safety and efficacy of therapeutic regimes, diagnostic tests and surgical interventions. The *GP Notebook* defines EBM as '*a discipline that formalises the long-practiced principle of basing clinical practice on scientific evidence*'. The ability to seek information, often from research, and to evaluate its merits and applicability therefore becomes an important requirement of today's medical practitioner. Such skills, along with being able to work as a member of a team, plan one's learning, manage one's time, generates hypotheses and design experiments have been reported to be core skills for engendering life-long learning in medical students (Whittle & Murdoch-Eaton, 2001).

How do we develop skills such as critical analysis and review, an academic approach to medicine and research methodologies in our students? Activities such as research, scheduled early in an undergraduate medical student's studies would certainly be one way. At the FMHS, community medicine projects, in which students investigate health and well-being issues relating to UAE communities, were introduced into Year 6 for the first cohort of senior clerks in 1992 and have remained an integral component of the clerkship. As the research profile of the new faculty developed, formal undergraduate research became part of the second year programme (Medical Sciences Course) in 2001. Initially, presumably because of their supervision experience of clerkship projects, many of the research topics were offered by Community Medicine faculty. Today, only a few years later, things are very different. Much of the supervision is overseen by biomedical scientists in the traditional pre-clinical disciplines of

Academic year	Types of projects (%)	Disciplines involved (%)	Faculty involved (%) *
2001/2	Laboratory: 27.3 Community: 27.3 **Other: 45.4	50.0 pre-clinical 37.5 clinical 12.5 medical education	33.4 pre-clinical 58.3 clinical 8.3 medical education
2002/3	Laboratory: 25.0 Community: 25.0 Other: 50.0	50.0 pre-clinical 50.0 clinical	53.8 pre-clinical 46.2 clinical
2003/4	Laboratory: 37.5 Community: 62.5	75.0 pre-clinical 25.0 clinical	66.7 pre-clinical 33.3 clinical
2004/5	Laboratory: 100	80.0 pre-clinical 20.0 clinical	90.0 pre-clinical 10.0 clinical
2005/6	Laboratory: 66.6 Clinical: 16.7 Community: 16.7	71.4 pre-clinical 28.6 clinical	57.1 pre-clinical 42.9 clinical
Average	**Laboratory: 51.3 Clinical: 3.3 Community: 26.3 Other: 19.1**	**65.3 pre-clinical 32.2 clinical 2.5 medical education**	**60.2 pre-clinical 38.1 clinical 1.7 medical education**

Table 1. Types of second year research projects and the disciplines of the supervisors. Projects were introduced into the curriculum in the 2001/2002 academic year. *Refers to discipline; **mixed, e.g. clinical/laboratory.

Mohammed and Abdulla Al Kuwaiti working in Chris Howarth's laboratory in the Faculty of Medicine and Health Sciences, one of nine colleges in the United Arab Emirates University.

anatomy, physiology, biochemistry and medical microbiology (Table 1). Projects are generally laboratory-based, with many involving rat and mouse models or tissue culture to study diseases such as diabetes and Parkinson's.

A recent audit of the first few years of undergraduate research has revealed that medical scientists are also largely responsible for the supervision of the summer vacation research, introduced soon after mainstream research projects (Table 2). Over the past year or two, increasing numbers of first year students are now starting their research project in the summer before they begin their second year of medical studies. This allows them 4-6 weeks of additional research time, leading to the collection of more meaningful data.

Each year, for 2-3 FMHS students who excel in research, a joint initiative of the FMHS and the British Council sponsors a visit to a research laboratory at a UK university (e.g. Leeds, Manchester, Glasgow, Bristol). The value of such an experience for a young medical student cannot be underestimated.

Opportunities exist for our students to present their research at public fora, locally and abroad. Apart from annual faculty and university events to showcase their research, the Gulf Co-operation Council (GCC) Medical Students' Research Conference rotates each year around the Gulf states of Oman, the UAE, Saudi Arabia, Bahrain and Kuwait. Some students choose to attend international conferences. Last year, a student who spent his summer at a UK research laboratory won a prize at the Young European Scientists' Symposium in Portugal. In March 2007, a group of 12 students attended the Leiden Medical Students' Conference, where one poster entitled *Teratogenic mechanisms of craniofacial malformations in mouse embryos* was awarded second prize. These experiences give our students an insight into life as a student in another country and another culture. Supervisors may, from time to time, present their students' work abroad, with due acknowledgement.

Some of our student research has appeared in peer-reviewed journals. As publications are a measure of scholarship, this will undoubtedly strengthen FMHS students' applications for residencies in North America, where many choose to specialise.

At the FMHS, although biomedical science research started from humble beginnings in 2001, it has developed into an integral component of the undergraduate medical curriculum, largely due to the enthusiasm and commitment of the medical science faculty. It has been recognised by external review committees as a valuable component of the curriculum that warrants continuation. Under the mentorship of the physiologists, anatomists, biochemists and microbiologists, we believe that our young students, by being introduced to biomedical research early in their studies, develop a number of skills that will ultimately assist them with their medical practice. In fact, this year, a second year project has sought to glean students' perceptions of the benefit of research on skills development and

Academic year (summer)	Types of projects (%)	Disciplines involved (%)	Number of Faculty staff involved (%)
2003	Laboratory: 57.7 Clinical: 19.2 Community: 3.9 Other: 19.2	50.0 pre-clinical 40.0 clinical 10.0 medical education	75.0 pre-clinical 20.8 clinical 4.2 medical education
2004	Laboratory: 94.7 Other: 5.3	66.6 pre-clinical 16.7 clinical 16.7 medical education	83.4 pre-clinical 8.3 clinical 8.3 medical education
2005	Laboratory: 74.1 Clinical: 7.4 Other: 18.5	54.5 pre-clinical 45.5 clinical	72.0 pre-clinical 28.0 clinical
2006	Laboratory: 81.0 Clinical: 4.7 Other: 14.3	14.3 clinical 85.7 pre-clinical	93.7 pre-clinical 6.3 clinical
Average	**Laboratory: 76.5 Clinical: 8.0 Community: 1.0 Other: 14.5**	**64.2 pre-clinical 29.1 clinical 6.7 medical education**	**81.0 pre-clinical 15.9 clinical 3.1 medical education**

Table 2. Extra-curricular faculty-based projects and the disciplines of supervisors (2003-2006).

on future studies and medical practice. Although the data are in the process of being analyzed, the indications are that students view their research experience as contributing to their development as medical practitioners.

We also believe that engaging junior students in the rigors of biomedical research provides firm foundations in the basic medical sciences that they require for their clinical years. Hopefully, this early experience will stimulate a research interest in some students, serving as a springboard for a career in clinical research, particularly into 'endangered' disciplines (Solomon *et al.* 2002; Halpain *et al.* 2005) – 'career pipelining', in the words of Halpain and his colleagues (2005).

The FMHS may be in the fortunate position of having small student numbers, allowing each learner to actively participate in one or more of the research projects of faculty members. Large student numbers in many UK and USA universities may not permit the same level of involvement. Notwithstanding, the move in the UK of a 'core curriculum' with special study modules is encouraging (Murdoch-Eaton *et al.* 2004). If research is offered as one of the special study modules, interested students will have an opportunity to participate. North American institutions too are beginning to appreciate the value of research in medical studies and many curricula now include research (Rhyne, 2000; Schor *et al.* 2005; Solomon *et al.* 2002). Some German universities recognised the need for research in medical studies many years ago, and a research dissertation has been a requirement for a medical degree for some time. This intensive research has contributed significantly to the productivity and scholarship of the institutions, with many students appearing as first authors on peer-reviewed publications (Dewey, 2003).

So, biomedical research for undergraduate students at the FMHS

Shaikha Al-Muhairi working in David Eisner's laboratory at the University of Manchester.

– from humble beginnings to an integral part of the medical curriculum, thanks to the commitment of a handful of biomedical scientists. We believe that by providing numerous opportunities for research for our students within and beyond the curriculum we are contributing to a more critical and informed cadre of medical graduates.

Michelle McLean
Chris Howarth
Medical Education and Physiology, Faculty of Medicine and Health Sciences, United Arab Emirates University

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Society for Endocrinology prize

Congratulations to Harry Leitch, an undergraduate medical student in the Department of Physiology, Development and Neuroscience at the University of Cambridge, who won first prize from the Society for Endocrinology for an essay on the role of kisspeptins in the reproductive axis. The title of his winning entry is *Re-engaging undergraduates with endocrinology – another role for kisspeptin*? For more details see http://www.endocrinology.org/news/. Harry's thoughts on what it was like doing a summer project were published in *Physiology News* (**67**, 41).

What happens to the central respiratory rhythm during breath-holding?

Michael Parkes considers some of the implications of the continuation of the central respiratory rhythm during breath-holding

Humans have virtually no voluntary control of their heart beating, but do have considerable voluntary control of breathing. For example, they can easily synchronise breathing to a metronome over the range of 5–30 beats per minute. There has always been a tacit presumption that humans stop their respiratory rhythm during breath-holding. Recent evidence shows, however, that this is not the case.

It is not yet possible to measure the central respiratory rhythm directly in humans. Recordings cannot yet be made from brainstem neurones with respiratory-related discharge, nor from the phrenic nerve. (Conversely, animal training has so far failed to elicit breath-holding experiments longer than about 5 seconds.) In humans, the activity of the central respiratory rhythm is normally inferred from respiratory motor output such as inspiratory pressure, airflow or chest movement. Obviously, such respiratory motor output stops during breath-holding, but this doesn't necessarily establish that the central respiratory rhythm has stopped.

In a classic study in 1963, Emilio Agostoni had three subjects swallow a catheter, enabling measurement of

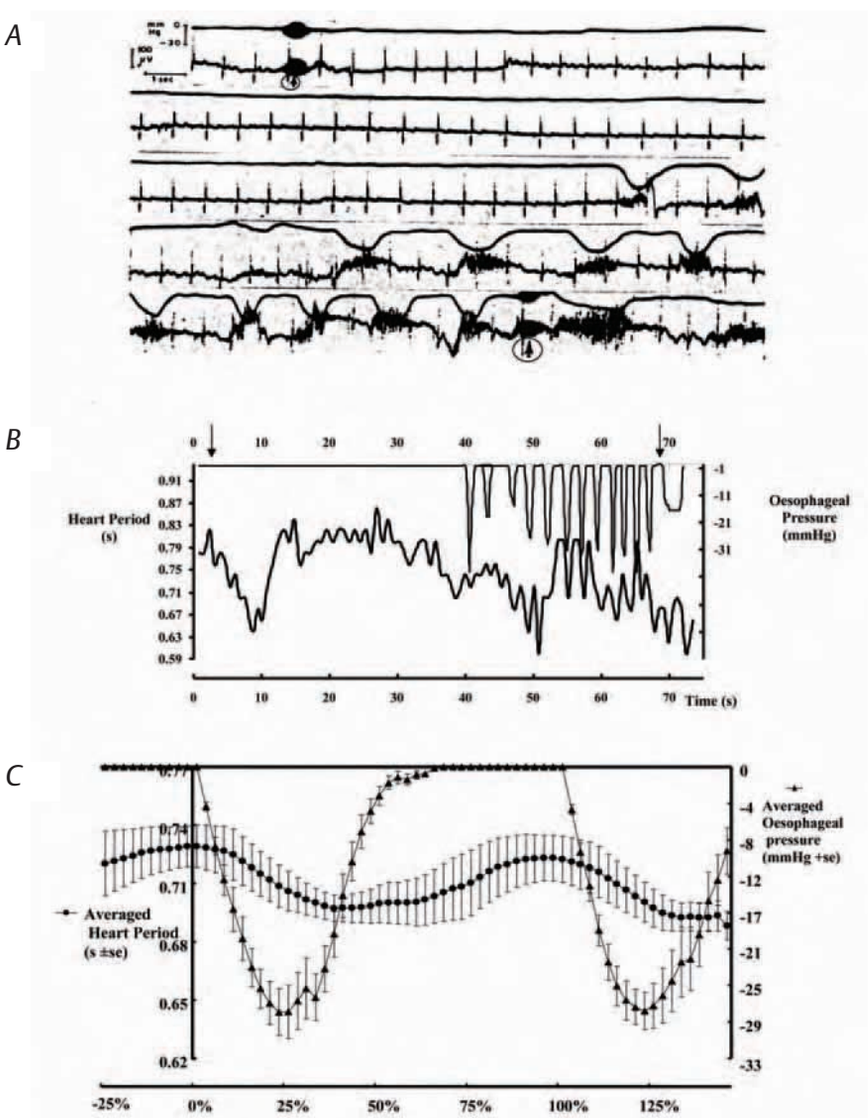

Figure 1. *A*, Appearance of rhythmic diaphragm EMG activity towards the end of breath-holding. Oesophageal pressure (upper trace) and diaphragm EMG activity (lower trace) in one 22 year old subject during breath-holding at resting lung volume in air. Used with the permission of Agostoni (1963) and the American Physiological Society. The start and end of the breath-hold are indicated by circled arrows. *B*, Sinus arrhythmia in 1*A*, from the start of breath-holding. Using a copy of the original record from 1*A*, kindly provided by Emilio Agostoni, I have measured the time of each R wave (to within 20 ms) in each ECG artefact to calculate instantaneous heart period as described in Cooper *et al.* (2004) and measured the time and size of each of the 12 oesophageal pressure waves. The start and end of the breath-hold are indicated by arrows. *C*, Some of the sinus arrhythmia in 1*A* is respiratory. I have sampled the instantaneous heart period and pressure waves from 1*B* every 2.5% of time between the start of each pressure wave and the next. I then averaged both over the 11 oesophageal pressure wave intervals during the breath-hold as described in Cooper *et al.* (2004). This shows that some of the sinus arrhythmia is respiratory, i.e. some sinus arrhythmia shows a similar relationship to rhythmic diaphragm activity (heart period decreases during inspiration) to that seen during eupnea (see Fig. 1*C* in Cooper *et al.*[2004]). Figs. 1*B* & 1*C* are reproduced with permission from Blackwell Publishing.

oesophageal pressure and electromyogram activity (emg). He showed (Fig. 1*A*) that rhythmic emg bursts appeared towards the end of the breath-hold. Since each burst was accompanied by a wave of negative pressure, the emg activity was believed to be recorded across the oesophagus from the diaphragm. Subsequent studies by William Whitelaw showed that the amplitude and frequency of these negative pressure waves increased towards the end of the breath-hold. Since PCO_2 rises linearly throughout breath-holding, these waves possess the CO_2 sensitivity characteristic of the central respiratory rhythm. These studies show that the central respiratory rhythm reappears before the breakpoint of breath-holding. They do not, however, establish whether the central respiratory rhythm suddenly reappears, or whether it had not stopped but was simply too difficult to detect at the start of breathing.

We have developed another approach to reveal the presence of the central respiratory rhythm, by using respiratory sinus arrhythmia. The factors contributing to sinus arrhythmia are complex. Animal studies show that these include effects of the central respiratory rhythm and of pulmonary inflation and its mechanical sequelae (including complex interactions with the baroreflex and atrial stretch). No study has established the precise contribution each makes to total respiratory sinus arrhythmia.

We therefore established first that the central respiratory rhythm does make a substantial contribution to sinus arrhythmia in unanaesthetised humans (Cooper *et al.* 2004). We did this by devising a regime of mechanical hyperventilation, where the central respiratory rhythm remained demonstrable in normocapnia from respiratory motor output (diaphragm emg activity recorded from the chest surface and from the shape of the inflation pressure waveform). We maintained normocapnia ($PetCO_2$ of 41 mmHg)

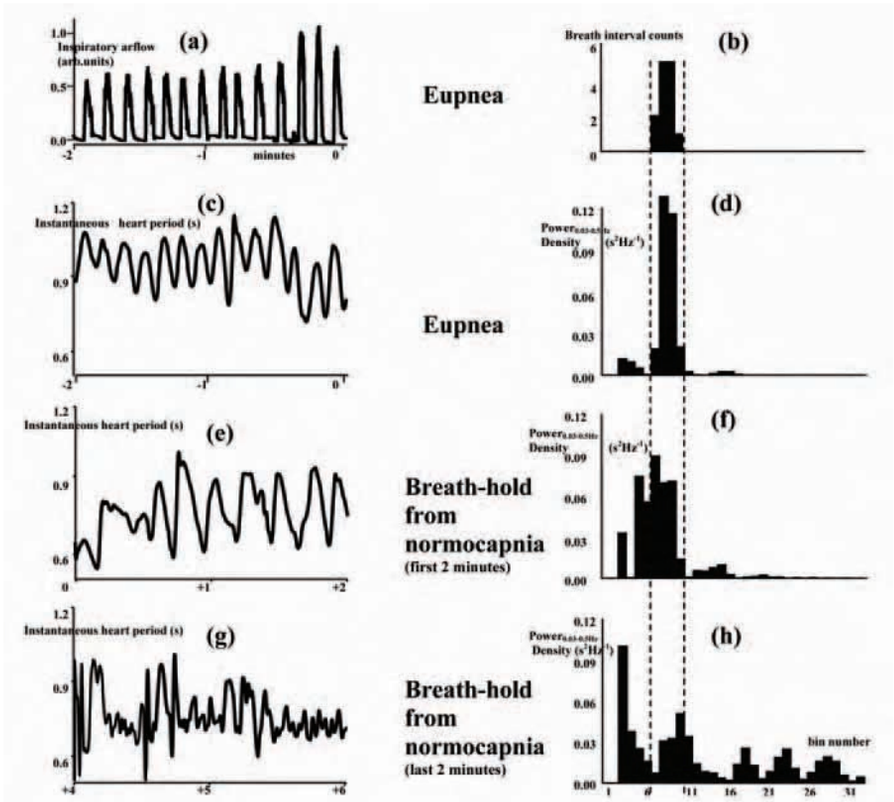

Figure 2. Sinus arrhythmia in the subject with the longest breath-hold (6.7 min) in normocapnia with preoxygenation at maximum inflation (Cooper *et al.* 2003), used with the permission of the American Physiological Society. (a) Eupnea immediately preceding breath-holding. (b) Distribution of the 13 breath intervals in (a) within the 30 bins describing frequency (0.03 –0.5Hz). The dotted line indicates his eupneic frequency range (bins 7–10). (c-h) Instantaneous heart period and its power 0.03–0.5Hz density spectra in eupnea (c-d), the first 2 (e-f) and last 2 (g-h) minutes of breath-holds from normocapnia (6 minutes). The horizontal scale in (b), (d) & (f) indicates each of the 32 bins describing 0-0.5Hz.

during hyperventilation by addition of CO_2 to the inspirate. In humans, hypocapnia augments the potency of the pulmonary stretch reflex but attenuates the central respiratory rhythm, so it is an ideal condition to reveal the predominant contribution to respiratory sinus arrhythmia. We induced hypocapnia (24 mmHg) by a surreptitious removal of CO_2 from the inspirate, which was imperceptible to subjects. We showed that during hypocapnia the rhythmic changes in pulmonary inflation were unchanged but the respiratory motor output disappeared i.e., the central respiratory rhythm was greatly attenuated. The fact that there was also a large reduction in sinus arrhythmia establishes that the central respiratory rhythm makes the predominant contribution to respiratory sinus arrhythmia in humans.

In some ways, breath-holding is an ideal way to reveal whether the central respiratory rhythm continues to cause respiratory sinus arrhythmia, because rhythmic pulmonary inflation and its mechanical sequelae are absent. There has been much debate about whether respiratory sinus arrhythmia does continue during breath-holding. *The Handbook of Physiology* seems to suggests that it does not, yet it is clearly evident in some early studies (e.g. Valentinuzzi & Geddes, 1974). Much of the debate arises because of the difficulties in using relatively short breath-holds (20–45 s). If some subjects happen to breathe naturally at relatively low frequencies (e.g. < 6 breaths per minute), there would be so few respiratory cycles that respiratory sinus arrhythmia may well be difficult to identify.

We avoided these difficulties (Cooper *et al.* 2003) by prolonging breath-hold duration to a mean of 4 minutes with preoxygenation. (Preoxygenation has the additional advantage of preventing the chemoreflex stimulation of heart rate that normally occurs during breath-holding.) Fig. 2(e) shows that sinus arrhythmia does continue from the start of breath-holding. This sinus arrhythmia is also CO_2 sensitive. The spectral power density measurements indicate that sinus arrhythmia moves to higher frequencies as pCO_2 increases throughout the breath-hold and that there is less sinus arrhythmia in breath-holds from hypocapnia.

In 2006 I was able to perform a similar analysis on some of Emilio Agostoni's 1963 data when he kindly lent me some of his original records. From enlargements I was able to measure sinus arrhythmia from the ECG artefacts and its relationship to the oesophageal emg and pressure waves (Parkes, 2006). Fig. 1*B* shows, in this 1963 data too, that sinus arrhythmia persists from the start of breath-holding. Furthermore, Fig. 1*C* shows that it coincides with the rhythmic emg and negative pressure waves when they appear. In the absence of direct measures of the central respiratory rhythm in humans, the persistence of CO_2-sensitive sinus arrhythmia throughout breath-holding provides the best evidence that the central respiratory rhythm does continue from the start of breath-holding.

This has a number of important implications for our understanding of basic human physiology.
First, humans clearly have less voluntary control of their central respiratory rhythm than was previously supposed. It would be far too dangerous to be able to stop the heart beating voluntarily. It now appears that humans also lack this level of control over their other vital rhythm. This, in turn, has interesting implications for our understanding of 'apnea' and 'central apnea' and their clinical diagnosis and treatment.

Second, many previous studies (particularly in cardiovascular control), have used breath-holding to study mechanisms in the presumed absence of the central respiratory rhythm. This presumption is no longer valid. All that is absent is rhythmic pulmonary inflation. Similarly, it is no longer correct to presume either that end-expiratory breath-holds stop the central respiratory rhythm in its expiratory phase, or that end-inspiratory breath-holds stop it in the inspiratory phase. Indeed, for breath-hold research, the lung volume itself may be the only important feature, not the means by which it is achieved.

Finally, the mechanism of breath-holding is not voluntary cessation of the central respiratory rhythm but is voluntary suppression of the expression of this rhythm. The latest techniques of brain imaging might be useful in identifying the location(s) of this suppression.

Michael J Parkes
School of Sport & Exercise Science, University of Birmingham, UK

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Molecular water pumps – or how water can move uphill across epithelia

How are water and glucose absorbed by the small intestine after a meal? In this situation the glucose concentration is high and the water concentration low in the lumen and water has to be transported uphill, into the body, against osmotic pressure differences of up to five atmospheres. The transport mechanisms responsible are molecular and can be stimulated to balance the severe dehydrations experienced in, for example, cholera

In order to live on land we must closely control and maintain our internal aqueous milieu. Each day the small intestine receives a total of about 10 l of water which originates from glandular secretions plus what is being ingested. This water and its contents of sugars, amino acids, salts etc. have to be absorbed during its passage through the intestine. This is done efficiently – only 0.1 l (1%) is lost to the outside. Clearly, diseases which upset this balance lead to fatal dehydrations. In the kidney the situation is even more dramatic. Each day, 180 l of plasma (four times our total body water!) is being filtered in the nephrons. Fortunately, most of this water is reabsorbed and only about 2 l lost in the urine. At present, there is no adequate explanation of how water is absorbed in the intestine and the kidney. Most models presume the existence of an intraepithelial hyperosmolar compartment, such as in the lateral intercellular spaces. Despite numerous investigations no such hyperosmolarities have been found yet.

Uphill water transport in the small intestine

A major stumbling block for epithelial models has been to explain uphill water transport, i.e. transport against an osmotic gradient. This problem is illustrated most clearly in the small

intestine just after a meal consisting of sugars.

In order to be absorbed, sugars are cleaved by local enzymes into monosaccharides such as glucose. In the process, the concentration of glucose becomes much higher and the concentration of water much lower in the lumen than in the blood plasma (Fig. 2, upper panel). Thus glucose could, in principle, be transported passively or downhill into the blood plasma. Water, in contrast, has to move actively or uphill in order to be absorbed. It has been established for more than a century that the small intestine is able to absorb significant amounts of water from a hyperosmolar solution. Indeed, the human small intestine can absorb water from luminal solutions that contain up to 250 mM of glucose in addition to the electrolytes (Pappenheimer, 1998) equivalent to uphill transport of water against an osmotic pressure difference of about five atmospheres. This ability is not unique for the small intestine. Even the very water-permeable epithelium of the kidney proximal tubule transports water uphill, although to a lesser degree. Key questions are therefore:

- why is water not lost into the intestinal lumen but instead transported into the plasma?
- what is energizing the water transport?
- how is the water transport linked to the glucose transport?

Molecular water pumps

To answer these questions, we have suggested that cotransporters function as molecular water pumps. In the human Na^+/glucose cotransporter (hSGLT1), for example, a wide range of experiments has shown that 250 water molecules follow the transport of 2 Na^+ ions and 1 glucose molecule in a strict stoichiometrical relationship; in the rabbit SGLT1 360 water molecules (Loo *et al.* 2002). As a result, these cotransporters can utilize the energy contained in the Na^+ gradient for the uphill transport of water. The tightness of the coupling between ions and water is emphasized by the fact that it works both ways: a gradient in water chemical potential can drive an uphill flux of ions in the same stoichiometrical ratio as above.

Figure 1 (left). Early days of studying water transport in *Xenopus* oocytes. Thomas Zeuthen is monitoring (crudely) the volume changes of an SGLT1-expressing *Xenopus* oocyte in the laboratory of E M Wright, UCLA in 1995. At present the resolution of the measurements is equivalent to an increase in oocyte diameter of 100Å which is close to the thickness of a lipid bilayer (*photo by D D F Loo*).

The idea of molecular water pumps originated from measurements in the choroid plexus epithelium where it was found that transport by the K^+/Cl^- cotransporter (KCC) was strictly coupled to transport of water (Zeuthen, 1991). Today, the idea is pursued by expression of co-transporters in frog eggs (*Xenopus laevis* oocytes), a technique that allows for the detection of minute water fluxes (Fig. 1). So far, we have found coupling between substrates and water in all Na^+-coupled cotransporters of the symport type. Artefacts such as conventional unstirred layer effects can be excluded due to the relatively high rates of diffusion inside the oocytes. How could the structural features and conformational changes in co-transporters give rise to cotransport of water? One model is an extension of the mobile barrier model first suggested by Mitchell (1990) and explained in Fig. 3. On this model a shift between closed conformations and conformations open to the outside or the inside of the membrane gives rise to a coupling between the transport of water and substrates.

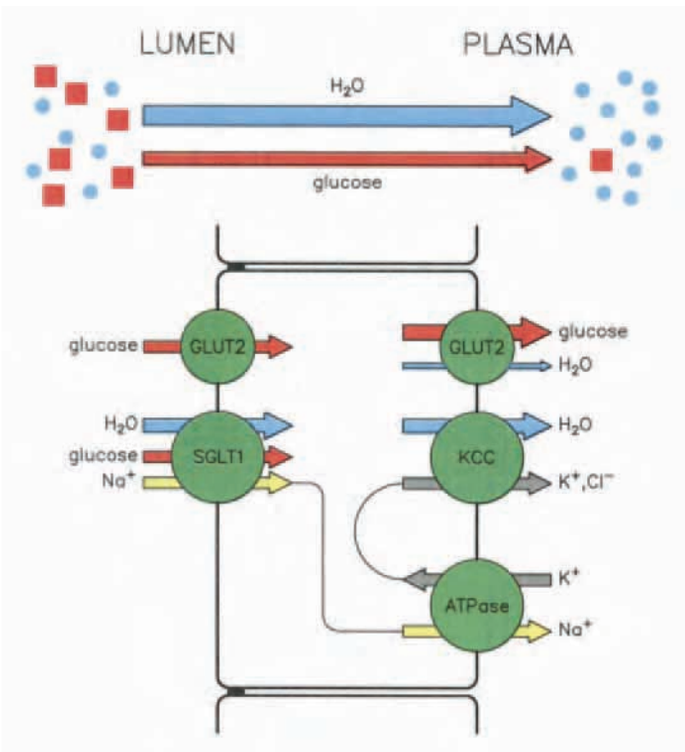

Figure 2. A molecular model of water and glucose transport in the small intestine just after a meal. Upper panel: after a meal the glucose concentrations (red squares) are high and water concentrations (blue circles) low in the lumen compared to plasma, yet both substances are absorbed. Lower panel: the transport of water is coupled to the Na^+ and glucose transport in the luminal SGLT1 and to K^+ and Cl^- in the abluminal KCC. The energy for the uphill transport is derived from the Na^+/K^+ATPase. There is possibly a small water flux coupled to the efflux of glucose in the GLUT2 in the abluminal membrane. GLUT2 is present both in the luminal and the abluminal membrane during a meal. Between meals, GLUT2 is absent from the luminal membrane.

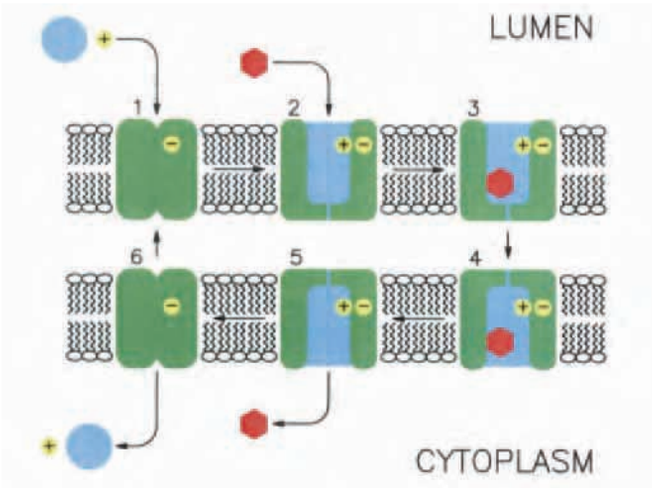

Figure 3. SGLT1 as a molecular water pump. It is assumed that the cotransport of Na+ ions (yellow +), glucose (red) and water (blue) takes place through a series of conformational changes (1-6). First, a Na+ ion binds and water enters the protein from the lumen to form an aqueous cavity (state 1 and 2). This allows the glucose to bind (state 3). The protein changes from an outside-open to an inside-open conformation (state 4). The glucose (state 5), and the Na+ ion and water (state 6) are expelled from the SGLT1 into the cytoplasm. As a result Na+, glucose and water are cotransported across the membrane. For clarity, only one Na+ ion is shown.

Interestingly, Mitchell did allude to a link between water movements and conformational changes: 'If, as seems likely, the mobile barrier mechanism involves the opening and closing of a cleft on either side of a substrate-binding domain, one might expect considerable hydrodynamic action as aqueous medium was sucked in and squirted out by the crevices.' Each step in the cycle suggested in Fig. 3 is well established for aqueous enzymes. Hexokinase, for example, looses and takes up 300 water molecules in the process of phosphorylating a glucose molecule. A clear picture of how the conformational changes are linked to water transport must await structural determination at the atomic level for each of the conformations shown in Fig. 3. So far, it is encouraging that a wide aqueous cavity has been found in the substrate binding conformation of a variety of cotransporters.

Molecular mechanism of water and glucose transport across epithelia

How could molecular water pumps explain the uphill transport of water and the downhill transport of glucose just after a meal (Fig. 2)? Glucose absorption into the cell takes place via two transporters, the SGLT1 and the luminal glucose monoport GLUT2. Interestingly, this GLUT2 is only active in connection with a meal (Kellett, 2001). In this location the GLUT2 is rather tight to water (Zeuthen *et al.* 2007). Glucose finally leaves the cell and enters the plasma via the ubiquitous, abluminal GLUT2.
The water absorption requires energy. The influx of water takes place via the SGLT1 and is energized by the coupling to the influx of Na^+, which, in turn, derives its energy from the Na^+/K^+ATPase. The final step of water transport, from the cell into the plasma, is energized by a coupling to the downhill efflux of K^+ and Cl^- by the K^+/Cl^- cotransporter (KCC), which is found abluminally in most epithelia. Again, the energy is provided indirectly by the Na^+/K^+ATPase. In addition, there is preliminary evidence for a coupling between glucose and water transport in the GLUT2 working in the efflux direction (Zeuthen *et al.* 2007). The model in Fig. 2 shows only the molecular water pumps; in a given epithelium there are, of course, plenty of other transporters. The kidney proximal tubules, for example, are richly provided with water channels (aquaporins) taking advantage of the *downhill* gradient for water absorption across this epithelium *in vivo*.

Cholera and oral rehydration therapy (ORT)

Cholera toxins give rise to major secretions of fluid into the intestinal lumen. The patients experience severe diarrhoea and may loose 3 l or more of water each day. The underlying molecular mechanism is the insertion of a Cl^- channel in the luminal membrane. Fortunately, the situation can be countered by the stimulation of the absorptive mechanism outlined in Fig. 2. The two molecular mechanisms, the secretory and the absorptive, are, so to speak, matching each other while the infection is treated. The absorptive component is maximized by ORT: The patient drinks a solution containing 75 mM of NaCl, 75 mM of glucose, and water. This stimulates the uptake of water by the SGLT1 to a degree that compensates for the amount secreted; the uptake of 120 gram of NaCl and 200 gram of glucose would be linked to the uptake of 4 to 5 l of water. ORT is estimated to save more than half the children suffering from severe diarrhoea.

In conclusion, the molecular model of epithelial water transport gives a rational background for the understanding and treatment of life threatening dehydrations.

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Thomas Zeuthen

Nordic Centre for Water Imbalance Related Disorders, The Panum Institute, University of Copenhagen, Denmark

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Exercise is a good habit for bowel health


Ozgur Kasimay (left) and Berrak Yegen

A substantial body of evidence verifies the benefits of regular physical activity on physiological and psychological well-being. Mild and moderate physical activity is associated with a lower incidence of mortality from any cause, especially from heart disease. Physical activity is beneficial to health because it reduces the risk of cardiovascular and endocrine diseases, improves bone and muscle conditioning and lessens anxiety and depression (Bi & Triadafilopoulos, 2003). It also diminishes high blood pressure, metabolic disorders such as diabetes mellitus, colon and rectal cancers, estrogen-dependent cancers of the ovary, breast, and endometrium (Woods, 1998), osteoporosis and mental depression; moreover, it can improve the quality of life.

The impact of exercise on the gastrointestinal system can be either beneficial or harmful for the gastrointestinal tract (Bi & Triadafilopoulos, 2003), depending partly on training intensity. The occurrence of gastrointestinal symptoms such as heartburn, nausea, vomiting, abdominal cramps, diarrhea and gastrointestinal bleeding is common during vigorous sports, causing the athlete to limit performance by reducing exercise intensity or duration (Peters *et al.* 2001). On the other hand, regular exercise at a low intensity may have protective effects on the gastrointestinal tract. Mild physical activity reduces abdominal distension by increasing intestinal gas clearance and transit of intraluminal gas (Villoria *et al.* 2006). The combination of diet and exercise therapy is effective in protection against reflux, as gas retention during rest decreases with dietary fibers and physical exercise. In particular, regular exercise at low intensity may reduce the risk of gastrointestinal disorders such as gastrointestinal hemorrhage, inflammatory bowel disease, cholelithiasis, diverticular disease or constipation.

Lack of physical activity is closely related to the development of colon cancer. There is strong evidence that regular exercise not only reduces the risk of developing colon cancer by up to 50%, but it also lowers the risk of death from colon cancer. A cohort study of Swedish men demonstrated that leisure-time physical activity was inversely associated with colorectal cancer risk (Larsson *et al.* 2006). Similarly, a Danish cohort study that aimed to assess the association between leisure-time physical activity and incidence of cancer in the general population of adult men and women, showed a significant inverse relationship between vigorous physical activity and cancer of the ovary for physically active women, while vigorous activity was associated with a non-significant lower risk of colon cancer in men (Schnohr *et al.* 2005). These results support a role of physical activity in reducing the risk of colon, rectal and ovarian cancer.

Ulcerative colitis is an idiopathic inflammatory bowel disease (IBD) with diffuse, recurrent inflammation of the colon and rectum, which is predominantly characterized by cycles of acute inflammation, ulceration and bleeding of the colonic mucosa. There is a long history of observations suggesting that psychological stress contributes to the course of IBD (Maunder, 2005) and that chronic stress increases the severity of intestinal inflammation (Gulpinar *et al.* 2004). Considering the improvements in psychological outcomes (i.e., depression, anxiety, mood states) reached by habitual

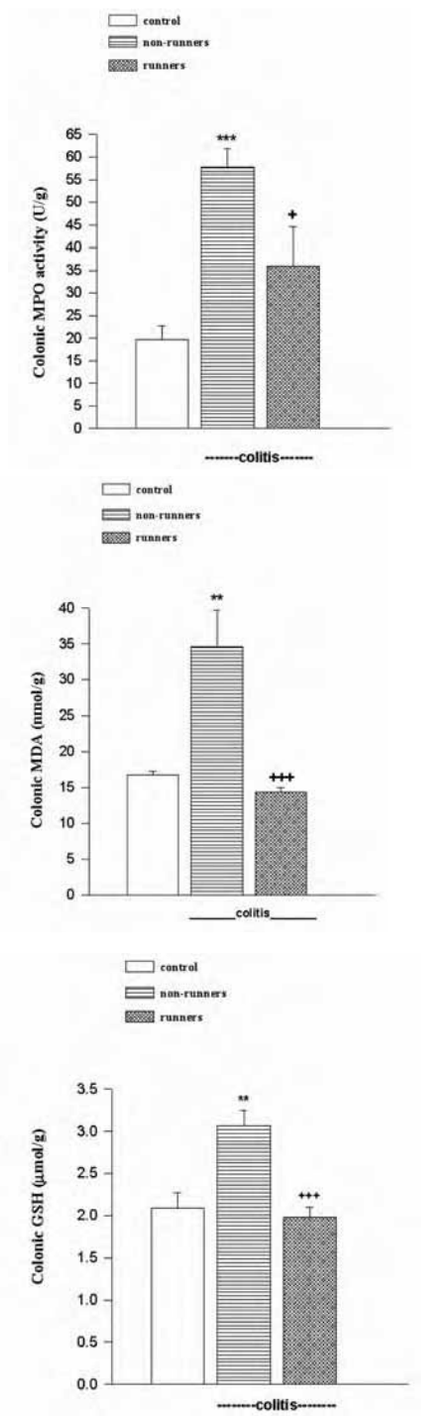


Figure 1. The protective effect of exercise on oxidative injury of the colon, as indicated with a depression of neutrophil infiltration to the colon (MPO, myeloperoxidase activity – top panel) , an inhibition of lipid peroxidation (MDA, malondialdehyde – middle panel) and an elevation in tissue antioxidant level (GSH, glutathione – bottom panel). $^{**}p < 0.01$ and $^{***}p < 0.001$, compared to control rats, $+p < 0.05$ and $+++p < 0.001$, compared to non-runner colitis group.

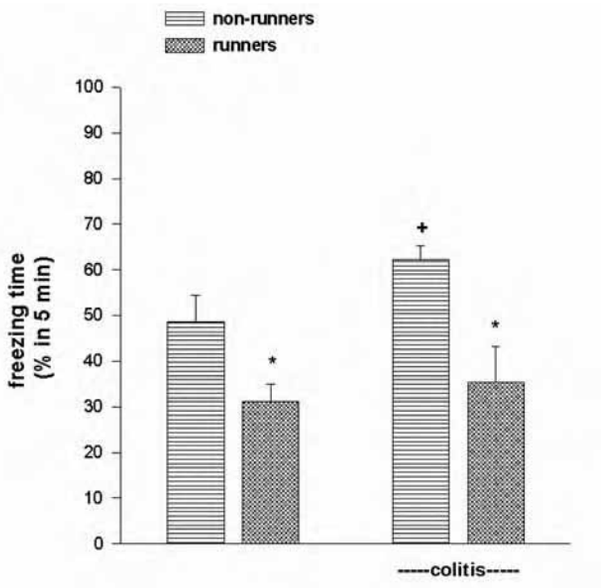


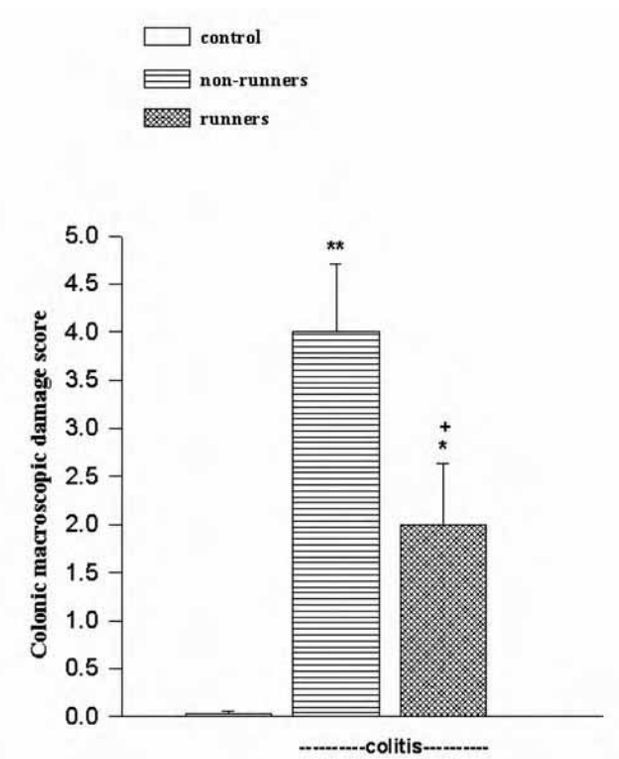
Figure 2 (left). The anxiolytic effect of exercise on rats with colitis. Colitis increases the freezing time, indicating increased anxiety level. $^{*}p < 0.05$, compared with corresponding non-runner rats, $+p < 0.05$, compared with non-runner control group.

Figure 3 (below). The protective effect of exercise on colonic injury as assessed macroscopically. $^{*}p < 0.05$ and $^{**}p < 0.01$, compared with control rats, $+p < 0.05$, compared with non-runner colitis group.

exercise (Byrne & Byrne, 1993), a number of studies has investigated the preventive effect of physical activity on IBD. Sonnenberg (1990) showed that sedentary and physically less demanding occupations were associated with a higher risk of inflammatory bowel disease than were physically more demanding occupations. Furthermore, the results of a case control study comparing incidence rates of IBD showed a reduced risk for physically active patients with Crohn's disease or ulcerative colitis. However, in another study active Crohn's disease patients had a high risk (Klein *et al*. 1998). Suggested underlying mechanisms in this preventive effect were the stress-reducing effects of physical activity and changes in local neuro-immuno-endocrine effects (Loudon *et al.* 1999). In accordance with these studies, we demonstrated that physical activity attenuates the severity of the colonic inflammation by a neutrophil-dependent mechanism (Fig. 1, top panel), by attenuating the oxidative tissue damage, by reducing lipid peroxidation (Fig. 1, middle panel) and by enhancing the antioxidative enzyme activity on the oxidative injury of the colon (Kasimay *et al.* 2006). Our results also support the fact that depletion of colonic glutathione is one of the major factors permitting lipid peroxidation and subsequent colonic damage.

Since increased physical activity prevented colonic glutathione depletion, it appears that exercise supports the maintenance of antioxidant capacity in protecting the colonic tissue against oxidative stress (Fig. 1, bottom panel).

Exercise-induced increases in aerobic fitness were shown to have beneficial short-term and long-term effects on psychological outcomes (DiLorenzo *et al.* 1999). Similarly, physical activity was postulated to reduce disease activity and perceived stress in IBD patients, while general well-being and quality of life were improved (Loudon *et al.* 1999). Among the possible explanations for psychological outcomes are the direct effects of neurotransmitters (e.g., serotonin) in the brain that function to elevate mood (McDonald & Hodgdon, 1991). We recently demonstrated that regular exercise attenuates the anxiety of stressed animals. However, in accordance with previous studies demonstrating that psychological stress might amplify intestinal inflammation (Collins, 2001), severity of colitis was



enhanced as the level of anxiety was exaggerated. On the other hand, the degree of anxiety was reduced (Fig. 2) in regularly exercised rats that had significant attenuation of colonic inflammation (Fig. 3).

Exercise should be considered as a non-pharmacological intervention in controlling the course of inflammatory bowel diseases, specifically during stressful conditions that would trigger the exacerbation of the symptoms. In order to benefit from physical activity, including the health of the gut, people should perform moderate exercise at moderate intensity for 30 minutes/day at least 3 days/week. Regular exercise may not only help us attain a longer life, but also more years living independently with a better quality of life.

Ozgur Kasimay
Berrak Ç Yegen
Department of Physiology, Marmara University School of Medicine, Istanbul, Turkey

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Central CO_2 chemoreception: how can it be done without the perfect receptors?

Central CO_2 chemoreception is a vital sensory function believed to be carried out by specific CO_2 chemoreceptors. Recent studies suggest that brainstem neuronal networks may be able to achieve high CO_2 sensitivity and a wide sensing spectrum by common pH-sensitive ion channels and synaptic interactions

Only a handful of sensory functions remain without cellular identity. Central CO_2 chemoreception is one of them. Since it was first described almost a half century ago, tremendous efforts have been devoted to identify the central CO_2 chemoreceptors (CCRs). We now know their likely locations in certain brainstem nuclei in which several types of CO_2-chemosensitive neurons have been observed. We even know some potential cellular and molecular mechanisms for CO_2 sensing. However, the identity of the CCRs remains uncertain. As a result, several phenomena observed in central CO_2 chemoreception are rather controversial.

The ideal CCR cells would be highly sensitive to CO_2, project to respiratory-modulated neurons, and dictate systemic CO_2 responses. However, experimental evidence supporting the existence of such typical sensory cells is lacking. In contrast, neurons with various CO_2 chemosensitivity are found in many parts of the medulla and pons, although their functional significance is still not fully understood (Richerson, 2004).

The search for molecular CO_2/pH sensors has led to a number of candidate molecules in the past decade (Jiang *et al*. 2005). Studies involving transgenic mice, however, indicate that CO_2 chemoreception appears normal in animals lacking

one or other of these putative sensing molecules, such as 5-HT_{2a} receptor, TASK-1 channel and P2x receptor is disrupted (Linden *et al*. 2006; Popa *et al*. 2005; Rong *et al*. 2003). This raises the question as to how the results from previous physiological studies on these sensing molecules can be explained.

Perhaps the most paradoxical phenomenon in central CO_2 chemoreception is how the high CO_2 sensitivity and a wide sensing spectrum are achieved. The respiratory neuronal networks are highly sensitive to CO_2 over a wide sensing range (pCO_2 20–90 mm Hg), allowing a 20–30% change in systemic ventilation with a minute increase (by 1–2 mm Hg) in pCO_2 (Feldman *et al*. 2003). The high sensitivity and wide sensing spectrum cannot be produced by a single pH sensing molecule.

As shown in Fig. 1, the pH sensitivity of a molecule is determined by the steepness of its pH titration curve. The steeper the curve (corresponding to a high 'h' value in the Hill equation), the narrower the pH-sensing range. Thus, a highly pH-sensitive molecule tends to work in a rather narrow pH range. On the other hand, the sensitivity becomes low if it senses pH in a broad range.

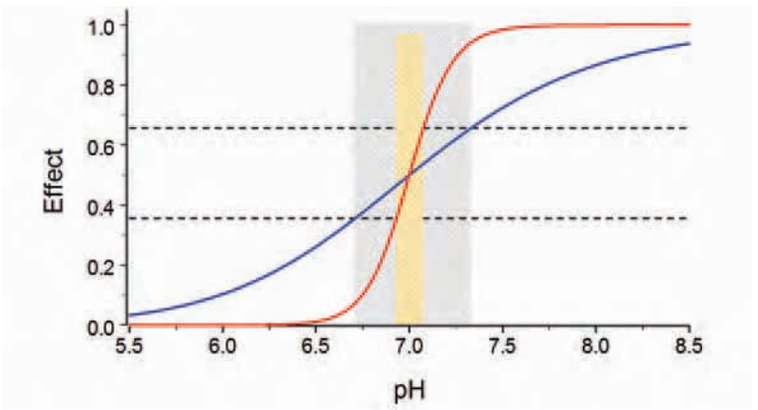

Figure 1. The pH-effect relationship (e.g. on an ionic current) is described with the Hill equation: $Y = I_{max} / (I_{max} + (pKa / X)^h)$, where Y is the effect on amplitude, I_{max} the maximum effect, pKa the pH value at 50% activation, X the pH levels, and h the Hill coefficient. Blue curve: pKa = 7.0, h = 1. Red curve: pKa = 7.0, h = 4.0. The grey shaded area is the pH spectrum covered by the blue cure, and the yellow is the pH spectrum for the red cure. Both are calculated as a 30% change in Y.

Therefore, the sensor molecule that is supreme in both sensitivity and spectrum does not seem to exist.

How does the respiratory neuronal network resolve the high sensitivity versus wide spectrum paradox? To address this, it is necessary to have a preparation that allows observation, as well as manipulation, of the cell-intrinsic membrane properties and neuronal interactions in their networks. For the latter simultaneous recordings from multiple neurons are essential. Thus, we have made primary neuronal cultures in a multi-electrode array (MEA) dish. Still in its infancy, the preparation has several weaknesses such as the loss of anatomical identity and the reduction in network components. Despite these problems, it is a useful preparation for the studies of both intrinsic membrane properties and synaptic interactions as well as simultaneous and repetitive recordings from multiple neurons.

Using the MEA technique, we studied the paradox of high sensitivity versus broad spectrum. We have found that cultured brainstem neurons retain their high CO_2 chemosensitivity in a broad sensing range in the MEA dish (Fig. 2). Blockade of inward rectifier K^+ (Kir) channels disrupts neuronal sensitivity to moderate hypercapnia and hypocapnia, whereas inhibition of TASK channels abrogates the neuronal response to more severe hypercapnia. These are consistent

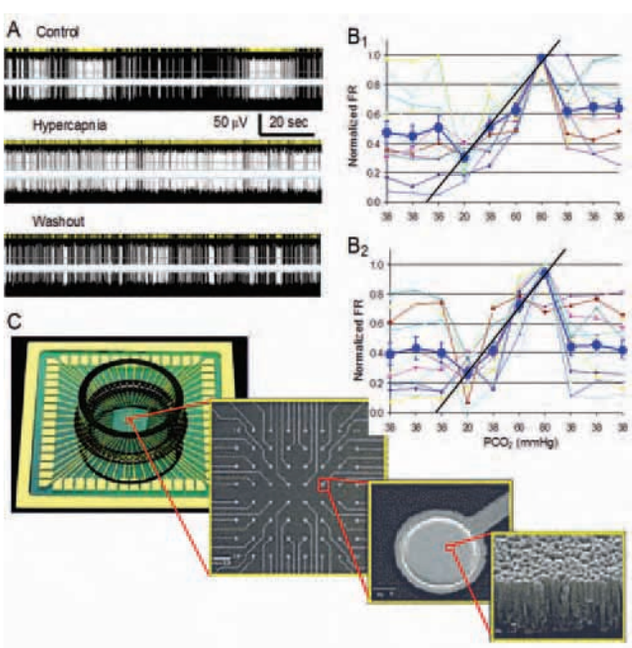

Figure 2. CO_2 chemosensitivity of cultured brainstem neurons studied in multi-electrode arrays (MEA). *A*, A single unit was recorded from one channel of an MEA dish. The unit was stimulated reversibly with an exposure to 10% CO_2. *B_1*, Thirteen units were recorded in another MEA dish. The firing rate (FR) of these units was modulated by CO_2 in a concentration-dependent manner. A linear response in the FR was seen in PCO_2 20–80 torr. Note that each thin coloured line indicates a unit, and the average of all units is shown as the thick blue line with large solid circles (means ± s.e.). The FR response can be described with a linear equation as shown with the straight black line, and the C slope value is 0.011. *B_2*, The response was reproducible as seen with repetitive exposure in a 24-hr interval with the C value 0.011. C, An MEA dish viewed in different magnifications.

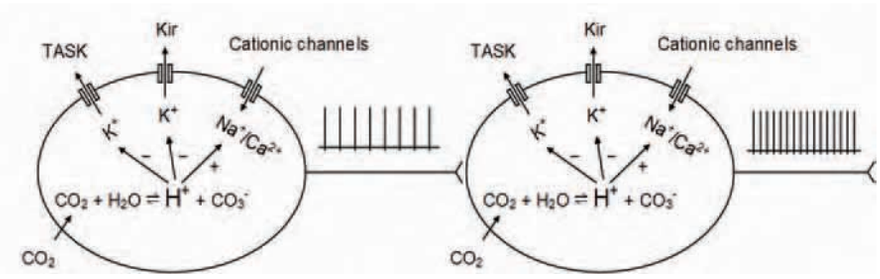

Figure 3. Schematic of CO_2 sensing in two neurons. Both cells express CO_2/pH sensitive ion channels. These sensing molecules work in parallel and cover different pH ranges allowing the cell to depolarize with an increase in ambient pCO_2 at various levels (parallel process). The cell on the left projects to the other with an excitatory synapse. Since both cells are CO_2 chemosensitive, the response of the post-synaptic cell is enhanced with these cells in a serial network (serial process). Note that for simplification other sensing molecules are not included. Abbreviations: Kir, inward rectifier K^+ channels; TASK, two-pore domain K^+ channels.

with the pH sensitivities of the heteromeric Kir4.1-Kir5.1 and the TASK-1 channels, both of which are expressed in the brainstem, suggesting that the broad PCO_2 spectrum can be covered by multiple sensors (Su *et al*. 2007). Since these molecules work in parallel for the detection of PCO_2 levels in the same cells, we termed this sensing the ‘parallel process’ (Fig. 3).

Although the parallel arrangement of multiple sensors helps neurons to preserve the CO_2 sensitivity of each sensor, these K^+ channels do not appear to be sensitive enough to transduce a change of 1–2 mm Hg PCO_2 into a 20–30% change in cellular activity. We have calculated the possible effect of the pH-sensitive Kir channels on membrane potentials, and found that at best they can produce a depolarization of ~1.5mV / 1 mm Hg PCO_2. Clearly, the high CO_2 sensitivity may not be produced by the primary sensory neurons alone. Therefore, we included neuronal network properties in our studies. We have found that CO_2 chemosensitivity is greatly reduced when neurons are isolated from their networks, suggesting that the CO_2 chemosensitivity relies on not only the cell-intrinsic sensing mechanism, but also on neuronal interactions through synaptic transmission. Indeed, our results show that several major excitatory neurotransmitters critical for respiratory control are involved in chemosensing synaptic transmission (Su *et al*. 2007). With intact network connections, some neurons increase their firing rate by 20–30% with a rise in1 mm Hg PCO_2, suggesting that an amplification mechanism by pre- and post-synaptic neurons exists, which we termed the ‘serial process’ (Fig. 3).

With the demonstration of the parallel and serial processes of CO_2 chemosensitivity, we may find explanations for other controversial phenomena:

- why are the optimal CCRs hard to find? The systemic CO_2 response can be fulfilled by neurons in several CO_2-chemosensitive nuclei and their synaptic connections with respiratory neurons through signal amplification, but may not be accomplished by individual cells without the signal amplification;

- why are there so many CO_2-chemosensitive neurons? The signal amplification may involve a large number of interneurons, motor neurons and peripheral sensory neurons as well if they are CO_2-chemosensitive;

- why does knockout of a likely CO_2 sensing molecule impose very few adverse consequences to the system? The overlap in the spectrum of the sensing molecules may allow them to compensate for the functional defect of each other, a likely evolutional strategy for the reservation of certain vital functions such as control of respiration.

Of course, these observations need to be verified in other preparations, as they were made in an *in vitro* preparation of reduced neuronal networks. It is the reduced network preparation however that allows us to make a leap from individual cells to neuronal networks. We believe that with the emphasis on both individual neurons in several brainstem CO_2 chemosensitive nuclei and the neuronal networks, better preparations can be developed, which will surely lead to an improved understanding of central CO_2 chemoreception.

Chun Jiang, Junda Su, Asheebo Rojas

Department of Biology, Georgia State University, Atlanta, Georgia, USA

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Inspiratory muscle training as an ergogenic aid: credible at last?

Recent evidence points to an important role for respiratory muscle work in limiting exercise tolerance. Alison McConnell (below) proposes that it is time to start thinking differently about the role of inspiratory muscle training in alleviating this limitation

For most of the 20th century, exercise physiologists viewed the respiratory system as one that was the exception to the rule of symorphosis (structural design is matched to functional demand). After all, at sea level, oxygen transport is not limited by the diffusion of oxygen, and human beings appear to have considerable breathing reserve, even at maximal exercise. What, then, might be the point of training the respiratory pump muscles? The past decade has witnessed a considerable advancement in our understanding of the limitations imposed by respiratory muscle work, as well as providing insights into the mechanisms by which specific training of the respiratory pump elicits improvements in exercise tolerance.

Research on respiratory muscle training (RMT) has its origins in the 1970s, when early studies sought to demonstrate that the respiratory muscles were responsive to specific training. Later research sought to evaluate the potential benefits of such training with respect to exercise tolerance in both healthy people and patients with respiratory disease. Up until the late 1990s, the literature on RMT in healthy young adults was contradictory to say the least (McConnell & Romer, 2004b). Poor research design and inappropriate outcome measures had created a very 'mixed bag' of data that only served to confirm the perceived wisdom that breathing does not limit exercise tolerance. The picture was equally murky with respect to research on patients with lung disease, but interpretation of this body of research was also hampered by a lack of rigorously conducted studies (see McConnell & Romer, 2004a). A turning point in research on RMT came during the late 1990s, when more reliable methods of training became more widely used (specifically pressure threshold training) and a more rigorous approach to research design was adopted.

My own group has had a particular interest in the potential application of

RMT as an ergogenic aid, i.e. as a performance-enhancing intervention in athletes. An important aspect of research on the ergogenic properties of interventions is to establish outcome measures that are not only reliable, but also have the external validity to make them relevant to athletic performance. In this context, time trials (performance against the clock) provide both validity and, in the right hands, reliability. The disadvantage of time trials is that the effect size of a performance change is generally very small (< 5%), which means that participants must have excellent pacing skills and be accustomed to reproducing truly maximal time trial performances.

The first study to examine the influence of RMT on time trial performance used rowing as the exercise modality, and chose well-trained oarswomen as participants (Volianitis *et al.* 2001). The advantage of using well-trained athletes is that the reliability of their time trials is very high. A single-blind placebo-controlled design was implemented, and performance was assessed using two rowing ergometer time trials in the laboratory. The 11 week period of pressure threshold inspiratory muscle training (IMT) increased the distance covered during a 6 minute all-out effort by 1.9% above placebo, and the time taken to cover 5,000 m improved by 2.2%. In addition, there were accompanying reductions in blood lactate concentration and breathing effort during a separate ergometer trial incorporating a series of fixed work rates. Finally, IMT also reduced inspiratory muscle fatigue induced by the 6 minute time trial (from an ~11% deficit in strength to ~3%), despite the fact that the athletes had completed the time trial more quickly.

In a subsequent study on well-trained male cyclists, the rigour of the research design was improved by using a double-blind placebo-controlled design, and by quantifying both the IMT and the whole-body training (Romer *et al.* 2002). The latter was to ensure that any changes in exercise performance could not be ascribed to changes in the athletes' whole-body training. The performance outcome measures in this study were a 20 km and a 40 km cycling time trial, which were simulated under laboratory conditions. After the 6 week period of IMT, the 20 km and 40 km time trial performances improved by 3.8% and 4.6% above placebo, respectively. The study also demonstrated attenuation of both respiratory and whole-body effort sensations, and a reduction in exercise-induced inspiratory muscle fatigue. Thus, in both oarswomen and male cyclists, IMT induced a range of physiological and perceptual changes that were consistent and repeatable.

Neither the rowing nor the cycling study demonstrated any change in maximal oxygen uptake (VO_2max) after IMT, which is consistent with observations of other investigators (see McConnell & Romer, 2004b). Some exercise physiologists interpreted this finding as a weakness of the studies; after all, how could training the respiratory pump increase exercise performance without increasing maximal oxygen uptake? Of course, a change in VO_2max would have completely contradicted our understanding of the factors that limit oxygen transport, since the participants were not diffusion limited. For a time it was thought that the answer may lie in a change in the lactate threshold, which is the other key mechanism by which exercise performance improvements are normally achieved following whole-body training. However, in a carefully

conducted study we later showed that inspiratory muscle training did not improve the lactate threshold (McConnell & Sharpe, 2005).

These observations led to the conclusion that the mechanism underlying the apparent ergogenic effect of IMT must lie outside our conventional view of training-induced improvements in performance, i.e. it was not due to improvements in VO_2max and/or the lactate threshold. During this same period of the 1990s, Jerry Dempsey's group at the University of Wisconsin was undertaking some outstanding and elegant research into the influence of respiratory muscle work upon exercise tolerance. A review of this research was published in *Physiology News* (**65**, 25–27) and will not be rehearsed again here – suffice to say Jerry Dempsey and his colleagues have now provided very convincing evidence for the existence of an inspiratory muscle metaboreflex that can result in a blood flow 'steal' from the locomotor muscles. Could inspiratory muscle training be exerting its ergogenic effect by delaying or attenuating this reflex?

Hitherto, studies of the inspiratory muscle metaboreflex had been confined to models that studied vascular responses to the metaboreflex in either the resting limb, or during whole body cycling at maximal exercise. Thus, there was evidence that fatiguing inspiratory muscle work was capable of inducing vasoconstriction in the resting limb, and under conditions where cardiac output was maximal. However, it was unclear whether the metaboreflex could override the functional hyperaemia of exercise under conditions where there was cardiac output reserve. Furthermore, even if the metaboreflex did operate under such conditions, it was far from clear whether IMT could modulate its operation.

In our most recent study we have examined these questions using an isolated human lower leg model (McConnell & Lomax, 2006). Our basic premise was that if the inspiratory muscle metaboreflex induced a functionally meaningful reduction in limb vascular conductance, then the resulting impairment of limb blood flow should accelerate limb fatigue.

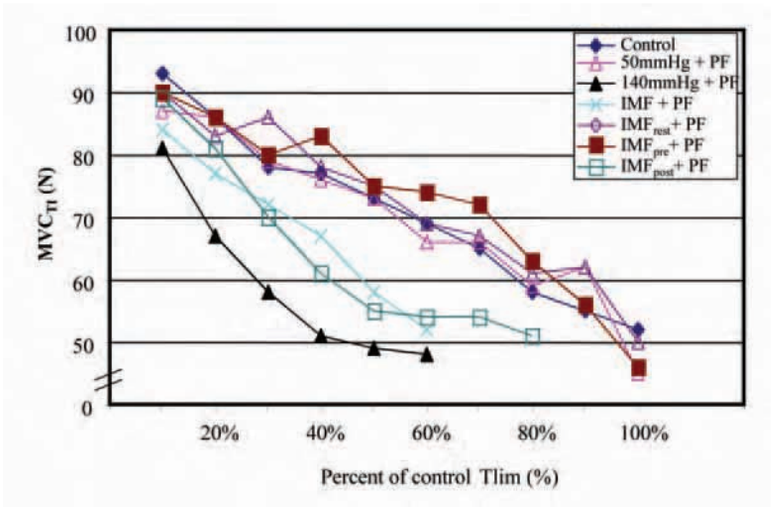

Figure 1. Comparison of the fatigue profile of the plantar flexors.
Note: MVC_{TI} = maximal voluntary contraction force with superimposed twitch; Tlim = time limit of plantar flexion (time to decrease below 50% of baseline MVC_{TI}); PF = plantar flexion; IMF = inspiratory muscle fatigue; 50 mmHg and 140 mmHg = mechanical blood flow occlusion with cuff inflation to 50 mmHg and 140 mmHg; IMF_{rest} = 30 min rest after IMF; IMF_{pre} = IMF at 60% of pre-IMT inspiratory muscle strength; IMF_{post} = IMF at 60% of post-IMT inspiratory muscle strength.

Furthermore, if IMT modulated the reflex, then the fatigue profile of the limb should also be modulated after IMT. To validate our limb fatigue model (plantar flexion), we first assessed its sensitivity to mechanical restriction of blood flow. In addition, we confirmed the ability of a fatiguing inspiratory muscle-loading protocol (IMF) to activate the inspiratory muscle metaboreflex. Following this, a number of manipulations of the pre-plantar flexion conditions were implemented: (1) a bout of IMF immediately prior to the plantar flexion, and (2) an identical bout of IMF followed by a 30-minute period of rest (to allow the metaboreflex to dissipate) before plantar flexion. After a 4 week period of IMT, condition (1) was repeated. In addition, we implemented a final condition in which the intensity of the inspiratory muscle loading was increased to account for the training-induced improvement in inspiratory muscle strength.

When plantar flexion was preceded immediately by IMF, the rate of plantar flexor fatigue was accelerated (Fig. 1). When a 30 minute period of rest was given between the IMF and plantar flexion, the fatigue profile was not significantly different to control. Similarly, after IMT, the same bout of IMF failed to induce any change in the rate of plantar flexion fatigue. In contrast, when the intensity of the IMF was increased to take account of the training-induced improvement in strength, the rate of plantar flexion fatigue was once again accelerated. These data support the notion that the inspiratory muscle metaboreflex operates at exercise intensities where there is cardiac output reserve. Furthermore, they suggest that IMT changes the threshold of inspiratory muscle work required to elicit the vasomotor response to activation of this metaboreflex. Thus, the most important determinant of the functional repercussions of inspiratory muscle work appears to be the relative intensity of that inspiratory muscle work.

In summary, RMT research has been hampered by the results of some poor studies that have generated contradictory data. In addition, there has been a natural scepticism about an intervention that appeared to fly in the face of exercise physiologists' understanding of the role of the respiratory pump in oxygen transport. However, respiratory muscle work has far wider repercussions than were previously appreciated, and it is now known that these muscles contribute to both the metabolic demand and sensory experience of exercise. Recent studies suggest that IMT generates improvements in exercise tolerance through two main mechanisms, which are probably also interlinked:

(1) attenuation of effort sensations (exercise feels easier after IMT) and (2) attenuation of the inspiratory muscle metaboreflex leading to a preservation of limb blood flow during exercise.

The role of RMT in enhancing exercise performance in athletes, as well as exercise tolerance in patients with dyspnoea, increased work of breathing, and/or circulatory limitations (e.g. chronic obstructive pulmonary disease, chronic heart failure) has been made considerably more credible by newly acquired insights into the wider consequences of exercise-induced inspiratory muscle work.

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Alison K McConnell
Centre for Sports Medicine & Human Performance, Brunel University, Uxbridge, UK

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Limitation to exercise performance at altitude – where is peripheral muscle fatigue important?

You might think the answer is 'where it hurts', but there is much more to it. Markus Amann explains

We have previously proposed that neural afferent feedback associated with peripheral locomotor muscle fatigue exerts an inhibitory influence on the central motor drive resulting in a centrally mediated limitation of exercise. This regulatory mechanism appears to be valid from sea level up to moderate altitudes (Amann *et al.* 2006a; Romer *et al.* 2007). More recently we have shown that the magnitude of this inhibitory peripheral feedback limiting central motor drive is significantly less at exhaustion in severe hypoxia, although exercise performance is limited even more (Amann *et al.* 2007). These observations suggest that, beyond moderate altitudes, other sources of inhibition of central motor drive start to outweigh the limiting effects of peripheral muscle fatigue and its associated inhibitory feedback (Fig. 1).

However, before going into further details of our newly proposed fatigue theorem, we will take a few steps back to recapitulate and reflect on some of our earlier findings. Based on strong correlative data, we think that sensory afferent feedback, originating in the fatiguing locomotor muscle, back to the CNS is a key determinant of the conscious (and/or subconscious) regulation of central motor drive (i.e. exercise performance). We believe in a strong link between 'peripheral' (i.e. biochemical changes *within* the muscle) and 'central' fatigue (reductions in CNS motor drive to the working muscle) (Amann *et al.* 2006a). Furthermore, we think that the magnitude of this inhibitory neural feedback is proportional to the magnitude of peripheral locomotor muscle fatigue, which in turn is highly sensitive to arterial O_2 content (C_aO_2) (Amann *et al.* 2006b), and consequently acts as a dose-dependent trigger of central fatigue. In lay terms: the lower the O_2 transport to the working legs during exercise the faster your locomotor muscle fatigue, the greater the inhibitory feedback to the CNS, the less the magnitude of central motor command and the greater the limitation to exercise performance.

Members of the John Rankin Laboratory of Pulmonary Medicine: Markus Amann (far right), Jerry Dempsey (middle) and our Medical Director Marlowe Eldridge (second from left). Also two friends on a short visit, lab alumnus Lee Romer (Brunel University, UK, far left) who assisted with the study and UW Program Specialist Margaret Rankin, youngest daughter of our laboratory's founder.

The purpose of such a regulatory feedback mechanism is presumably to protect the muscle from an 'excessive' development of peripheral fatigue beyond a critical threshold or 'sensory tolerance limit' (Gandevia, 2001). Based on a series of experiments during which we altered the inspiratory O_2 fraction (F_IO_2) to simulate various altitudes, we demonstrated that this regulatory mechanism is crucial in hyperoxia and up to a level of acute hypoxia equivalent to an altitude of approximately 4,000 m (Amann *et al* 2006a; Romer *et al.* 2007). After these initial studies, the following questions arose naturally: what happens if the mountaineer continues to climb beyond this altitude? Is the exercise-induced magnitude of peripheral locomotor muscle fatigue and/or the rate of development of fatigue of these muscles still as important a regulated variable at extreme altitudes? Or does the priority change and other organ systems, like the brain, take over the hierarchy of regulated variables due to the increased threat associated with severe systemic hypoxemia induced by exercise beyond moderate altitudes?

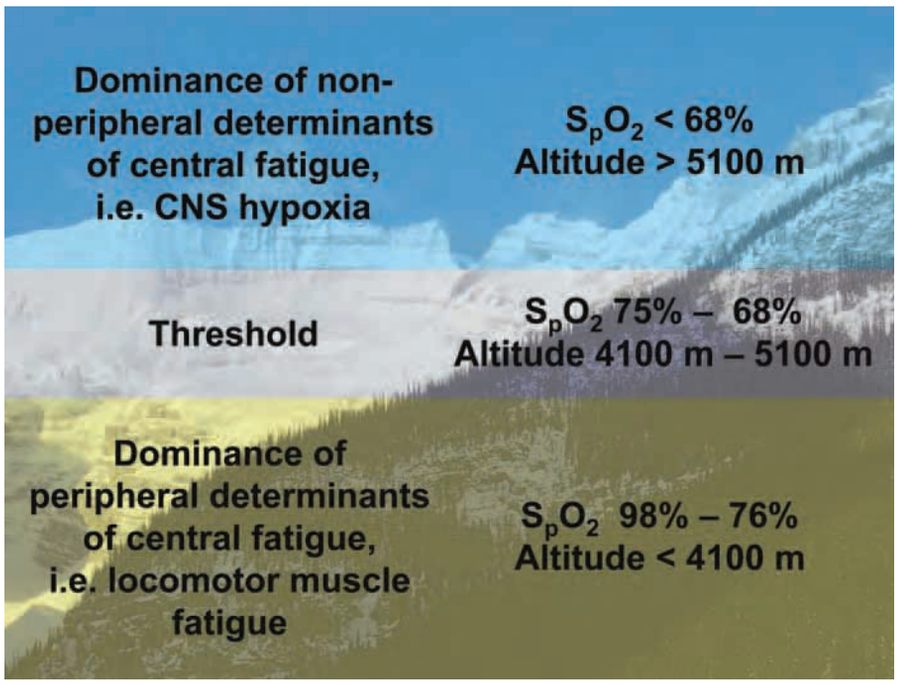

Figure 1. Haemoglobin saturations (S_pO_2) and associated estimated altitudes subdivided in three zones. The yellow zone indicates the range at which peripheral locomotor muscle fatigue and associated neural feedback is thought to be the main determinant of the reduction in central motor drive. The blue zone indicates the altitude at which CNS hypoxia presumably dominates the development of central fatigue. The 'grey area' illustrates the range of arterial oxygenation at which the switch from a predominant effect of peripheral fatigue to a predominant effect of CNS hypoxia might occur. The background picture was taken by the author at the lakefront of the Fairmont Chateau Lake Louise Hotel (Alberta, Canada) during the 2007 Hypoxia meeting.

Previous reports in the literature have already implied that severe CNS hypoxia may result in inhibitory effects on central motor drive (Kayser *et al.* 1994; Calbet *et al.* 2003). These conclusions were drawn from the observation that after cycling to exhaustion at great altitudes (> 5,000 m) the administration of 100% O_2 – thereby reversing the arterial desaturation – enabled the subjects to continue to exercise. Ultimately, these findings argue against the validity of our proposed regulatory mechanism (Amann *et al.* 2006a) (the development of central fatigue based on peripheral feedback) in extreme altitudes and indicate the existence of fast responding hypoxia-sensitive sources of inhibition of central motor drive. Now, how can our recently proposed regulatory mechanism and the indications of those 're-oxygenation' experiments be tied together – is there a link? Is there a fluctuating impact on the development of central fatigue? How is the magnitude of the impact of each of these determinants of central fatigue regulated?

We have suggested that the relative effects of centrally *versus* peripherally originating impairments of central motor drive (i.e. limitations in exercise performance) change with the level of convective O_2 transport as affected by acute hypoxia (Amann *et al.* 2007). Subjects were instructed to pedal against a heavy intensity fixed workload to task failure in normoxia, moderate and severe hypoxia (F_IO_2 0.21, 0.15, and 0.10, respectively). Clear criteria for task failure (drop in pedal cadence below 70% of self-selected target cadence for ≥5 s) and exhaustion (drop in pedal cadence below 60% of self-selected target cadence for ≥5 s) were established prior to the study. When the subjects, unaware of the procedure, reached task failure in each condition, arterial hypoxemia was rapidly removed by surreptitiously switching to an F_IO_2 of 0.3 (re-oxygenation). A significant prolongation of exercise time to exhaustion was not achieved following re-oxygenation at task failure in normoxia [arterial hemoglobin saturation (S_pO_2) of ~94%] and moderate hypoxia (S_pO_2 ~82%). However, in severe hypoxia (S_pO_2 ~67%), re-oxygenation at task failure elicited a significant prolongation (+170 %!) of time to exhaustion.

Why this difference with severe hypoxia? At task failure in normoxia and moderate hypoxia peripheral locomotor muscle fatigue – assessed via changes in quadriceps twitch force (ΔQ_{tw}) as measured pre- versus post-exercise in response to supramaximal femoral nerve stimulation – has reached the individual critical threshold (ΔQ_{tw} from pre- to post-exercise of about

–36%). As expected, this magnitude of peripheral fatigue did not change further within the additional few seconds of exercise to exhaustion after re-oxygenation following either normoxia or moderate hypoxia. This is consistent with the literature indicating that re-oxygenation has no instant alleviating effect on the already induced magnitude of peripheral muscle fatigue. Interestingly, however, at task failure in *severe* hypoxia peripheral muscle fatigue was significant but only about two-thirds of the level of fatigue measured at task failure in normoxia and moderate hypoxia and therefore far below the individual threshold or sensory tolerance limit. Following re-oxygenation in severe hypoxia, subjects continued to exercise and peripheral fatigue continued to develop to the same level (critical threshold) as observed at exhaustion in normoxia and moderate hypoxia (ΔQ_{tw} about –36%).

So, what limits endurance exercise in normoxia and moderate hypoxia vs. severe hypoxia and why was there significantly less locomotor muscle fatigue at task failure in severe hypoxia? The data indicate that exercise- and altitude-induced arterial hypoxemia as experienced at sea level and up to moderate altitudes (~ 4100 m), *per se*, is not severe enough – *by itself* – to impose an inhibitory influence on central motor drive in healthy humans. The CNS at these altitudes 'allows' the development of peripheral locomotor muscle fatigue until the individual critical threshold – or sensory tolerance limit – is achieved. This then in turn curtails central motor output, presumably via strong inhibitory neural feedback to the CNS.

At severe altitudes (> 5100 m) the roles seem to be reversed. The level of arterial hypoxemia during exercise at these extreme altitudes imposes a severe threat to brain function itself, possibly operating via interference with cerebral neurotransmitter turnover. Accordingly, central motor output is constrained largely independent from any inhibitory afferent feedback originating in the periphery. This central inhibitory effect of severe hypoxia probably serves to avoid severe cerebral dysfunction far in advance of reaching the individual critical threshold of peripheral muscle fatigue.

Why is end-exercise peripheral muscle fatigue at exhaustion (following re-oxygenation at task failure) identical in all three conditions? At sea level and at moderate altitude, peripheral locomotor muscle fatigue rises all the way to the individual critical threshold. Exercise is thus, despite re-oxygenation at task failure, terminated via a reduction in central motor output to prevent further development of peripheral fatigue beyond the individual critical threshold. By reversing the arterial hypoxemia and CNS hypoxia at task failure in severe hypoxia, the constraint to exercise quickly vanishes, exercise can be continued and the locomotor muscles continue to accumulate fatigue until the individual critical threshold is reached.

To date we only have correlative data to support the role of peripheral muscle fatigue and associated inhibitory feedback on central motor drive. We are currently investigating the effects of a direct blockade of neural feedback originating in the exercising and fatiguing locomotor muscles on central motor drive and the development of peripheral muscle fatigue.

In summary, we believe the current data support the concept that the dominance of CNS hypoxia over peripheral muscle fatigue in influencing central motor output, and therefore exercise performance, occurs below a threshold level of acutely compromised O_2 transport. This level is represented by a range of 75–68% S_aO_2, or the corresponding acute exposure to altitudes of about 4100–5100 m.

Markus Amann
The John Rankin Laboratory of Pulmonary Medicine, University of Wisconsin-Madison Medical School, USA

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Significant increase in impact factors

The Society is pleased to announce a significant increase in the 2006 impact factors for both its journals. *The Journal of Physiology* has increased its impact factor to 4.407 (4.272 in 2005), with an increase in ranking from 10/75 to 9/76 in the ISI's physiology category. The impact factor for *Experimental Physiology* has increased to 2.339 (2.054 in 2005), and its ranking from 40/75 to 33/76.

For more news on The Society's journals, see p. 46.

Circulating ATP and ADP: important regulators of blood flow and platelet reactivity during exercise

Gennady Yegutkin (left) and José González-Alonso

Extracellular ATP and other nucleotides (ADP, UTP, UDP) are important signalling molecules in the cardiovascular system, where they induce diverse vasodilatatory, immunomodulatory and prothrombotic responses (Bours *et al.* 2006; Burnstock, 2006). These effects are mediated through G-protein-coupled P2Y receptors as well as via ligand-gated P2X receptors (Fig.1*A*), which are ubiquitously expressed on various cell types, including the vascular endothelium and haematopoietic cells. Subsequent to signal transduction, nucleotides need to be rapidly inactivated and vascular endothelial ectoenzymes nucleoside triphosphate diphosphohydrolase (NTPDase; known as ecto-ATPDase, CD39) and ecto-5'-nucleotidase/CD73 are considered the major regulators of the duration and magnitude of purinergic signalling in the vasculature (Bours *et al.* 2006). In contrast to traditional paradigms that focus on nucleotide-inactivating mechanisms, it has now become clear that 'classical' intracellular enzymes, adenylate kinase and nucleoside diphosphate kinase, are also co-expressed on surfaces of endothelial cells, lymphocytes and other cell types and finely control local nucleotide concentrations via backward ATP-regenerating pathway (Fig. 1*B*) (Yegutkin *et al.* 2002). The generated adenosine, in turn, has a non-redundant counteracting role in the attenuation of inflammation and mediates cardioprotective, vasodilatory, angiogenic and other responses via interaction with own G-protein-coupled receptors (Bours *et al.* 2006). Extracellular adenosine is then either transported into the cell by nucleoside transporters or further inactivated to inosine via ecto-adenosine deaminase reaction (Yegutkin *et al.* 2002). Together, the extracellular nucleotide turnover depends on functional interactions between distinct processes including:

- transient release of ATP, ADP and other agonists;
- triggering of signaling events *via* nucleotide- and nucleoside-selective receptors;
- ectoenzymatic inactivation;
- nucleoside uptake by the cell.

The concept of a purinergic signalling system is now widely appreciated, and studies on pathophysiology and therapeutic potential of extracellular purines represent a novel and rapidly expanding field (Burnstock, 2006). In particular, recent findings provide evidence for important roles of circulating nucleotides in the regulation of platelet reactivity, haemostasis and blood flow under exercising conditions. Regular exercise training is consistently

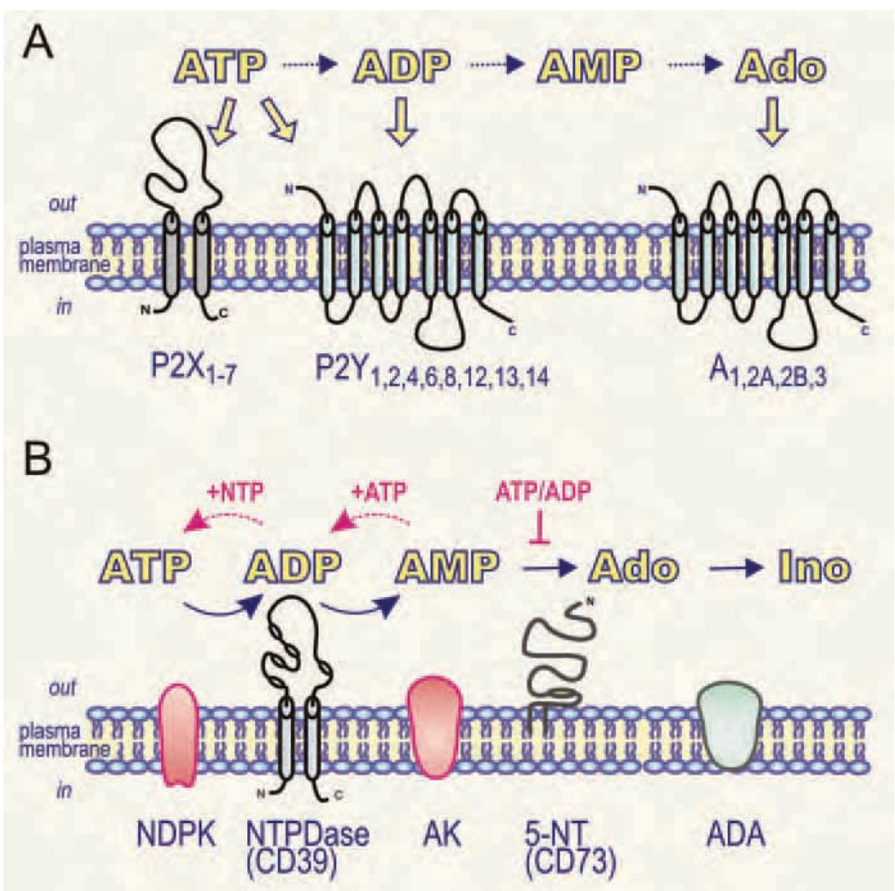

Figure 1. Turnover of extracellular nucleotides and nucleosides. *A*, Signalling effects of nucleotides occur through a series of ionotropic ATP-specific P2X receptors and metabotropic P2Y receptors that are classified by their affinities towards ATP, ADP and other putative nucleotide and nucleotide sugar agonists. Adenosine acts at four own nucleoside-selective receptors. *B*, Major exchange activities of extracellular nucleotides and their conversion into adenosine (Ado) and inosine (Ino). The elements of purine-inactivating chain comprise at least three ectoenzymes, NTPDase/CD39, ecto-5'-nucleotidase/CD73 and adenosine deaminase (ADA), whereas an opposite ATP-regenerating pathway is mediated via sequential adenylate kinase (AK) and nucleoside diphosphate kinase (NDPK) reactions.

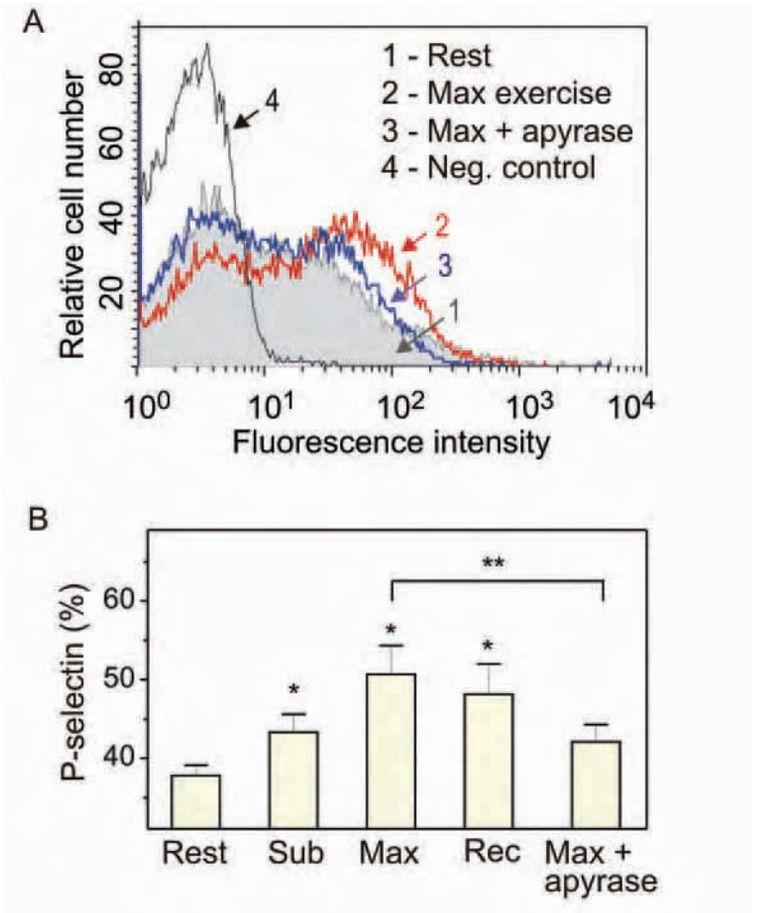

Figure 2. Plasma from exercising humans stimulates P-selectin expression on platelet surface. Blood was collected from the right atrium of endurance-trained athletes at rest, and during submaximal (*sub*) and maximal (*max*) cycling exercise and after 10 min of recovery (*rec*). *A*, Plasma samples were then co-incubated with platelets from resting volunteers while platelet activation was monitored by flow cytometry with anti-P-selectin monoclonal antibody. *B*, The percentage of P-selectin expression after platelet-plasma co-incubation was determined from the above fluorescence histograms (*$p < 0.05$ as compared with resting plasma; $n = 8$). Plasma from exercising subjects was also pretreated with exogenous apyrase (1 unit/ml) prior to addition to platelet suspension (**$p < 0.05$ as compared with non-treated plasma; $n = 4$).

associated with a variety of favourable alterations in cardio-vascular function, including reduced heart rate and increased maximal oxygen uptake, reduced blood pressure, activation of fibrinolysis and lower platelet activation. However, unfavourable haemostatic changes might occur at extreme exercise and environmental conditions that predispose to occlusive thrombus formation in coronary or cerebral vessels, and the extremely rare phenomenon of sudden cardiac death during exertion. Platelet activation and recruitment, followed by haemostatic plug formation, is generally initiated either via formation of thromboxane-A_2 by cyclooxygenase or secretion of ADP from dense granules with subsequent activation of platelet ADP-selective $P2Y_1/P2Y_{12}$ receptors. In turn, vascular endothelium controls platelet reactivity and prevents thrombus formation via three pathways, including nitric oxide and prostaglandin-I_2 synthesis and ADP scavenging via NTPDase activity (Burnstock, 2006).

Recently, we have shown that intravascular nucleotide turnover is acutely activated both in endurance-trained and sedentary subjects during performance of maximal cycling exercise (Yegutkin *et al.* 2007). A salient finding of this work is the demonstration that plasma from exercising humans, but not from resting control samples, up-regulates the expression level of the platelet activation marker P-selectin and that these prothrombotic effects can be attenuated after scavenging nucleotides by exogenous apyrase (Fig. 2). Subsequent reverse-phase high-performance liquid chromatographic analysis directly confirmed a significant increase in plasma ADP during exercise. This work additionally pointed to a role of ADP in platelet function beyond its immediate activity as a primary agonist. Probably, other synergistic factors like adrenaline (epinephrine) or some chemokines are released simultaneously with ADP that, in conjunction with the increased blood flow, would provide the stimuli for platelet activation during exercise.

While preferential activation of the coagulation cascade may predispose exercising subjects to the enhanced risk of intravascular thrombosis formation, other accompanying haemostatic changes such as activation of fibrinolysis and increased blood flow should work to counterbalance it. Blood flow and its surrogate oxygen delivery regulation are generally thought to result from the interplay of neural, myogenic and metabolic signals. A number of observations raised the possibility that purinergic signalling can also be implicated in the precise regulation of oxygen supply to contracting muscle under exercising and other hypoxic and hypercapnic conditions. Specifically, in addition to serving as an efficient oxygen carrier, the red blood cells act as sensors and controllers of local blood flow via transient release of ATP in proportion to the degree of haemoglobin deoxygenation (González-Alonso *et al.* 2002; Ellsworth, 2004). The released ATP subsequently induces a conducted vasodilatatory response upstream and regulates oxygen supply to contracting muscles via binding to the endothelial $P2Y_1/P2Y_2$ receptors and stimulation of vascular endothelium to release nitric oxide

and arachidonic acid metabolites (Ellsworth, 2004; Burnstock, 2006).

Identification of a network of soluble purine-converting enzymes freely circulating in the bloodstream adds another level of complexity to understanding the regulatory mechanisms of purine homeostasis within the vasculature. We have shown that two soluble nucleotide-inactivating enzymes, nucleotide pyrophosphatase/ phospho-diesterase (NPP) and NTPDase, constitutively circulate in the human bloodstream, and we have further demonstrated that their activities are transiently up-regulated during strenuous exercise by 20–25 and 80–100%, respectively (Yegutkin *et al.* 2007). The exercise-mediated increase revealed in serum NPP activity may allow the by-passing of the generation of a principal platelet-recruiting agent ADP, via direct conversion of circulating ATP into AMP and PP_i. Furthermore, concurrent activation of another soluble nucleotidase NTPDase might represent a novel and currently unappreciated effector system contributing, along with vascular endothelial NTPDases, to the termination of acute prothrombotic effects of ADP under hyperaemic exercising conditions.
Of note is the fact that the recombinant soluble form of human NTPDase/CD39 is currently considered a promising aspirin-insensitive antithrombotic drug, which potently inhibits platelet reactivity under various experimental prothrombotic conditions. Therefore, data on constitutive presence of soluble NTPDase in human blood and its up-regulation during exhaustive exercise may open up further research for future therapeutic applications of this major ADP-inactivating nucleotidase as a ‘natural antithrombotic enzyme’ for anti-platelet therapy in hypoxia-associated and other vascular diseases.

In summary, transient exercise-mediated increases in circulating ATP and ADP levels, together with concurrent up-regulation of soluble nucleotide-inactivating activities induced by endurance training, may represent an efficient control system that finely regulates both tissue O_2 delivery and platelet reactivity in healthy subjects. On the other hand, acute disturbances in the pattern of intravascular nucleotide turnover occurring during exhaustive exertion might contribute, in conjunction with other prothrombotic synergistic factors, to the enhanced risk of cardiovascular morbidity and mortality, especially in the elderly and sedentary subjects suffering from endothelial dysfunction and insufficient release of anti-platelet compounds.

Gennady G Yegutkin[1]
José González-Alonso[2]
[1]MediCity Research Laboratory, University of Turku and National Public Health Institute, Turku, Finland
[2]Centre for Sports Medicine and Human Performance, Brunel University, Uxbridge, UK

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The fallibility of referees

The following extract (see Bynum, 1976) from the 1941 Report of the Editorial Board of T*he Journal of Physiology* illustrates the pitfalls of the refereeing process.

Curious situations occasionally arise in the interplay between referees ’ judgements. One paper was considered completely unintelligible by the Board and the advice of a referee was sought. After much labour which entailed the rewriting of many paragraphs, the paper was returned to the office with the request that another referee should see it before it was passed to the press. So a second opinion was sought, and in his report the second referee had the misfortune to select as unintelligible the very paragraphs to the rewriting of which the first referee had devoted so much time and labour.

Bynum, W F (1976). A short history of The Physiological Society 1926–1976. *J Physiol* **263**, 67.

Further fallibilities of referees

An Australian visitor to the (then) Institute of Animal Physiology at Babraham told of his experience with an American journal soon after the war.

He thought it good training to make his student responsible for submitting the manuscript to the journal. When, after several weeks, no acknowledgement had been received he discovered the paper had been sent by surface mail (airmail was not necessarily the automatic choice in those far off days). A second copy was rapidly dispatched by air resulting, equally rapidly, in an airmailed rejection letter. News that the original manuscript had been accepted followed a week or so later.

Ann Silver
Cambridge, UK

Muscular dystrophy and the brain

Duchenne muscular dystrophy (DMD) is the second most common fatal genetic disease of human beings. It occurs with an incidence of about one in every 3500 live male births. The main characteristic of the disease is a progressive loss of skeletal muscle tissue, which eventually leads to the death of the afflicted boy. DMD was first described in the 17th century by the French physician Duchenne de Boulogne, and also in England by the British physician Edward Meryon. In his first description of the disease, Duchenne noted the boys often showed significant mental impairment. Studies in the latter half of the 20th century confirmed the mental impairment, with DMD boys having an average IQ of 85, and in addition, independently of their actual IQs, DMD boys have a poor performance in digit span, story recall, comprehension, serial position memory, reading and mathematical ability (Anderson *et al.* 2002). In boys, perhaps because of the severity of the skeletal muscle wasting of the disease and individual variability in the alterations of brain function, possibly reflecting the diversity of dystrophin gene mutation, the cognitive impairment has largely been overlooked. The *mdx* mouse, the most commonly used animal model of muscular dystrophy, also exhibits a range of behavioural and cognitive deficits (Anderson *et al.* 2002).

Dystrophin localization studies have identified at least seven isoforms of dystrophin, each with its own tissue-specific promoter, of which four are found in the CNS (Kunkel *et al.* 1985). Dystrophin is not uniformly distributed throughout the CNS, work on the *mdx* mouse shows that it is found in discrete areas of the brain and associated with specific neurons (Górecki & Barnard 1997). Clusters of dystrophin are most abundant on the soma and proximal dendrites of the pyramidal cells in cerebral cortex and hippocampus and on cerebellar Purkinje cells (Fig. 1*A*). In contrast to skeletal muscle, where dystrophin is distributed uniformly on the inside of the membrane, in neurons dystrophin is found in discrete punctate units localised at the postsynaptic density. Intriguingly, punctate clusters of dystrophin are not found at all postsynaptic densities, rather they are extensively co-localised with the $GABA_A$ inhibitory receptor in cerebral cortex, hippocampus and cerebellar Purkinje cells.

John Morley (left) and Stewart Head. John has recently been appointed Foreign Correspondent for *Physiology News*, along with John Hanrahan (McGill University, Canada).

Knuesel and colleagues (1999) elegantly demonstrated that in *mdx* mice the absence of dystrophin from the postsynaptic clusters does not eliminate clustering of the $GABA_A$ receptors, rather, it reduces both the number and size of clusters at the postsynaptic density of the inhibitory synapses. In our laboratory we used Western blots to show that there is no

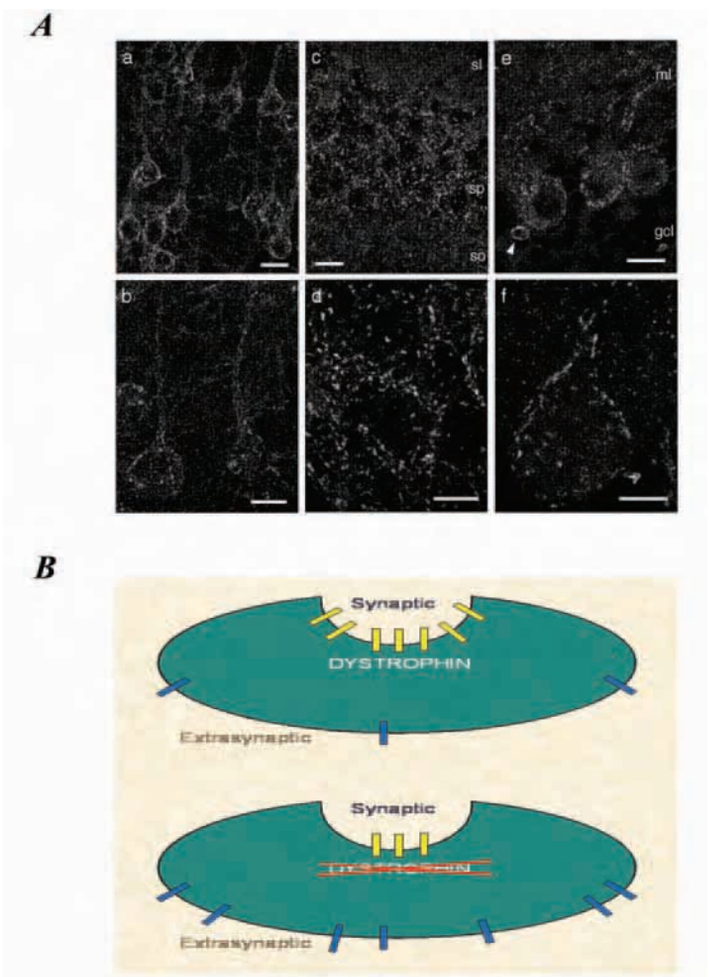

Figure 1. *A*, Distribution of dystrophin. (a and b) Layers III and V of rat neocortex, respectively; (c and d) hippocampus CA3 area; (e and f) cerebellum; immunofluorescence staining with the monoclonal antibody Dys-1. Abbreviations: sp, stratum pyramidale; so, stratum oriens; sl, stratum lucidum; ml, molecular layer; gcl, granule cell layer. Scale bars, 20 μm (a,c,e); 10 μm (b,d,f) (reproduced from Knuesel *et al*. 1999). *B*, In each case the large oval is a cartoon representation of a neuron, and the indentation in the oval represents the postsynaptic density. In the top oval, where dystrophin is present, it serves to aggregate the receptors into large clusters in the postsynaptic density. In the lower oval, where dystrophin is absent, there is a reduction in the size of the clusters present at the postsynaptic density and an increase in the number of extra synaptic receptors.

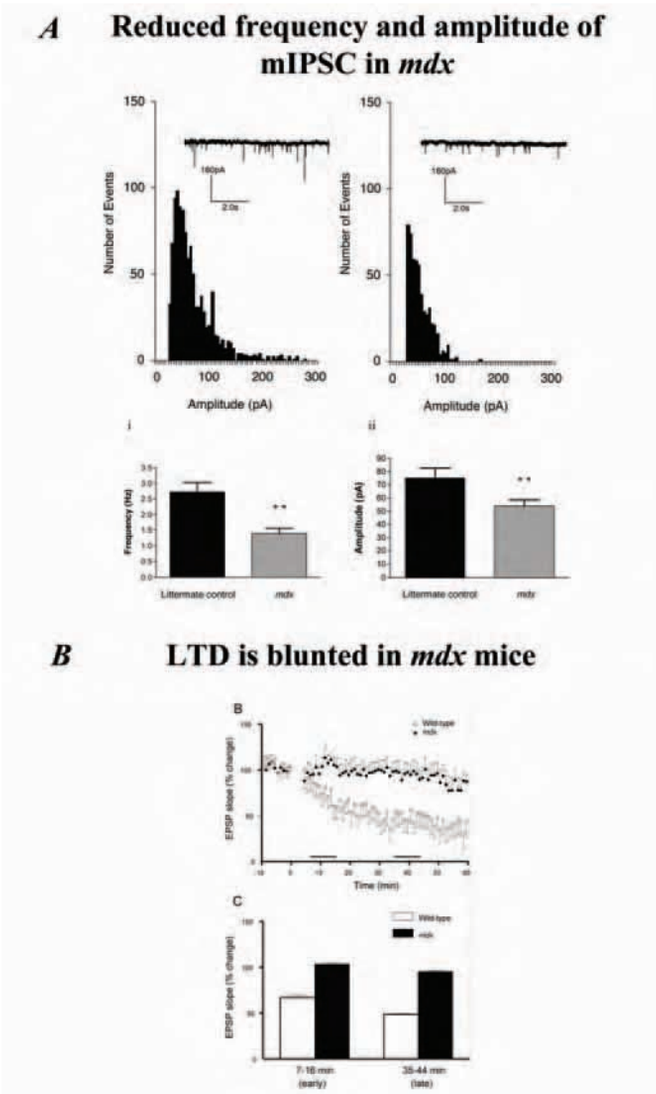

Figure 2. *A*, Miniature inhibitory post synaptic currents in littermate control and *mdx* Purkinje cells. Distribution of mIPSCs for a (i) littermate control and (ii) *mdx* mice Purkinje cell. The insert shows a section of the recording showing mIPSCs. The *mdx* mice has fewer large amplitude mIPSCs compared to littermate control. The bar graph shows the average frequency and amplitude of mIPSCs from littermate controls were significantly different from *mdx* mice (frequency, $p = 0.002$; amplitude, $p = 0.04$, two-tailed unpaired t-test). *B*, Long term depression in cerebellar Purkinje cells of control and *mdx* mice. The break in the graph indicates the period when the long term depression was induced. The horizontal bars above the abscissa illustrate the two 10 minute periods during which the EPSP slopes were averaged, and represent the early phase and late phase of long term depression. The bar graph displays the average slope for all control and *mdx* cells in the early and late phases following induction of long term depression.

difference between littermate control and *mdx* mice in the overall expression of $GABA_A$ receptor $\alpha 1$ subunit, which provides strong support for the suggestion that it is the clustering of receptors at the synapse that is affected in DMD, and that dystrophin may aid in trapping ion channels at the synaptic membrane and to aggregate them into large clusters for effective synaptic function. As a result, in dystrophic Purkinje cells it is likely that there is a substantially larger population of extrasynaptic $GABA_A$ receptors than in normal cells (Fig. 1*B*).

What role is dystrophin playing in the central nervous system? In skeletal muscle, it has been generally accepted that dystrophin plays an important role in maintaining normal $[Ca^{2+}]_i$ and, more controversially, has a mechanical function in stabilising the fragile lipid bilayer against stresses associated with skeletal muscle contraction. It seems unlikely that dystrophin has a similar mechanical role in neurons, however, its absence may alter $[Ca^{2+}]_i$ in neurons. As indicated above, in the CNS dystrophin is involved in the aggregation of large clusters of $GABA_A$ receptors at the postsynaptic inhibitory junction. In our laboratory we decided to use cerebellar brain slices from the *mdx* mouse to investigate the electrophysiological consequences of an absence of dystrophin from the Purkinje cell. The decision to use cerebellar Purkinje cells was an obvious one, primarily because Purkinje cells are the only neuron type in the cerebellum which express dystrophin and secondly because the Purkinje cells are large and easy to identify using infrared microscopy with differential interference contrast. Whole-cell patch clamping showed spontaneous miniature inhibitory post synaptic currents (mIPSCs) are reduced in frequency and amplitude in the dystrophic mice (Fig. 2*A*), a fairly predictable outcome of the reported reduction in the cluster size of the $GABA_A$ receptors. When we looked at an experimental model of synaptic plasticity, the effect of dystrophins absence was far from predictable. The Purkinje cell/parallel fibre synapse is a well studied model of long term depression (LTD). Using standard LTD induction paradigms we stimulated the parallel fibres in high-frequency bursts, while periodically mimicking the climbing fibre input to the Purkinje cell by depolarising the cell via a sharp intracellular microelectode. We deliberately chose to use the more classical sharp microelectrodes to record LTD in the Purkinje cells because we felt that if the absence of dystrophin altered the Ca^{2+} homoeostasis, this effect would be masked if the Purkinje cells were effectively $[Ca^{2+}]_i$ clamped by dialysing them with a whole-cell patch clamp electrode. To our surprise we found a marked blunting of the LTD in the dystrophic Purkinje cells (Fig2B). Our finding of altered long-term synaptic plasticity in the mouse model of DMD is supported by work on a dystroglycan protein knockout model of congenital muscular dystrophy which showed blunting of hippocampal long term potentiation (LTP) (Moore *et al.* 2002).

At first sight the blunting of LTD in the cerebellum of the dystrophin-deficient

mdx mice seems somewhat paradoxical, given LTD involves the excitatory AMPA receptors and dystrophin is associated with the inhibitory $GABA_A$ receptors. However, when we consider that dystrophin may be playing a role in $[Ca^{2+}]_i$ homoeostasis in the neurons, a pathological alteration of $[Ca^{2+}]_i$ homoeostasis will alter induction of LTD as $[Ca^{2+}]_i$ levels are critical in setting the thresholds for the induction of both LTD and LTP. We propose that one mechanism by which the$[Ca^{2+}]_i$ homoeostasis could be disrupted in the Purkinje neuron by the absence of dystrophin is if the larger population of extrasynaptic $GABA_A$ receptors alters the influx of Ca^{2+}. Fig. 1*B* illustrates what happens to the $GABA_A$ receptors when dystrophin is absent. We are currently in the process of using calcium sensitive dyes to test the extent to which $[Ca^{2+}]_i$ levels are disrupted in the mdx Purkinje cells.

Whatever the underlying mechanisms, a change in the electrophysiological characteristics of $GABA_A$ inhibitory receptors and the blunting of long term synaptic plasticity in dystrophin-deficient muscular dystrophy will lead to a disruption in motor control and motor learning, and may underlie some of the CNS problems reported in both in the *mdx* mice and boys with DMD.

Acknowledgement
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Stewart I Head[1]
John W Morley[1,2]
[1]School of Medical Sciences, University of New South Wales and [2]School of Medicine, University of Western Sydney, NSW, Australia

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Which book shall I read?

Perhaps the most frequently asked question by the first year medical students, it continues to puzzle many teachers of physiology. It was much easier to answer this in my student days, for there were only three books recommended! Abbreviated after the authors, these books- BT, SW and BDS- held sway for over decades in this country. Best & Taylor was the favoured tome of the top students who fancied some kind of closeness to the first author who, as a medical student assisted Banting and shared the Nobel Prize. Those who read Samson Wright continued to use it in clinical years, since many applied aspects were presented clearly. My favourite was the book written by Bell, Davidson and Scarborough. Written in simple English, I found it a pleasure to read this book. It featured simple diagrams to illustrate many concepts of physiology. Moreover it also included Biochemistry obviating the need of buying another book. All these books were available in bound form only and needed patience and effort to carry them around. Attempt to subdivide and rebind them, was considered a sacrilege! However many later generations of medical students resorted to such practice. Students seen reading any other book were looked down upon by their peers. Of course, there was ample time to read and understand the books, for in those days, the basic sciences were taught for two full years before entering the clinics.

Now, after three decades of teaching, I am still confronted by this question. Things have changed a lot. The medical council of India in its wisdom has restricted the basic science teaching to one year and every student appears to be in a hurry! I notice two distinct peaks in the frequency with which the old question is fielded. The first one, at the time of their entry into the medical school, when the students' enthusiasm about their studies is at the maximum. The second when they perceive that the exams are fast approaching! (the time of perception is variable though, from weeks to days) A number of good books are available for the serious minded. Bound volumes have gone out of fashion and given rise to paperbacks, pocket editions or concise concentrated physiology reviews. Some Indian authors have also tried their hand. One particularly well written book with a chapter on yoga appended, ceased publication because the writer turned a mystic. Curious case of an author falling victim to his own writings!

But it is the second peak that yielded a bumper crop of innumerable publications. In addition to the word physiology in their titles, these books display terms like instant, nutshell, guaranteed, last choice and panacea. One book, believe me, calls itself 'Pretty Darned Quick' physiology! The books are profusely illustrated with all colours and shades. The authors' titles and examinerships held in the past and at present, are printed in bold letters. They often carry the photograph of the author with spouse and children and an invariable proclamation that 'but for their co-operation, the writer could not have produced a better book'. (If you wish, omit the negative). In their prefaces, the word exam appears several times to impress the gullible. One such book was awarded a platinum disc for creating a record, for the number of sales! So when the perennial question is posed to me, I am really at a loss!

For an answer, of course.

J Prakasa Rao
Department of Physiology, Kasturba Medical College, Manipal, India.

Facing the media with animal research

Why are we so backward when it comes to going forward? In the past, a history of attacks and intimidation of Society Members by animal rights groups understandably encouraged a culture of reticence towards speaking out about work on animals. But the climate is changing. Sarah Bailey, a lecturer in the Department of Pharmacy and Pharmacology at the University of Bath (pictured below), recently went public with her work. Thelma Lovick talked to her about her experience of facing the media

Thelma Lovick (TL) What persuaded you to go public with your work?

Sarah Bailey (SB) When I worked in Bristol I had been involved in various events designed to communicate science to schoolchildren and the general public. I really enjoyed it but I'd never really talked about my own research. At that stage, I was still quite anxious about the animal issue.

TL So what changed your mind?

SB Well, in 2005 I went to a seminar on *Speaking out on animal research in the media* at the Science Media Centre in London and I was persuaded by their arguments that there is no real personal danger these days. I talked to Fiona Fox from the Science Media Centre and she thought the research I was doing might strike a chord with the public and excite their interest.

TL Tell me a bit more about your work.

SB Well, it all came about as a result of an invitation to spend Thanksgiving with Michelle Lane, a friend who was working at the University of Texas at Austin. Over the holiday period we decided to visit NASA in Houston and on the long car journey there, of course we started talking about work. I told her about my work on anxiety and depression and she explained about her work on retinoids, a class of compound that includes vitamin A and its derivatives, in relation to cancer. This class of compounds is well known for its role in the development of the nervous system, but not much is known about the actions in the adult brain. She asked me if I had heard about the reports

that Accutane (Roaccutane in UK), a popular treatment for severe acne, might cause depression in patients. The active ingredient is 13-*cis*-retinoic acid (isotretinoin), a retinoid. That really sparked my interest and we decided to carry out a scientific study to see whether Roaccutane could alter behaviour in mice. The outcome was that our work was the first to show in animals that chronic treatment with Roaccutane increases depression-related behaviours (O'Reilly et al Neuropsychopharmacology 31 (2006) 191-127).

TL When did you decide to go public with this finding?

SB After meeting Fiona Fox at the Science Media Centre event, she told me to get back in touch when the research was about to be published. I was anxious about going to the media with this work, in part because it involved animal studies, but also in case the findings were taken out of context or exaggerated by various interest groups for their own benefit. Fiona convinced me that the best approach was to 'set the agenda' myself by telling the story directly to invited science journalists in a media briefing at the Science Media Centre.

TL Scary.

SB Yes it was rather! I went to the Science Media Centre in London with Andrew, my Press Officer from the University of Bath. We handed out the press release and then had a question and answer session with the journalists. I was still nervous that they would challenge me about why I was using animals ... but they never did. They just asked me about the science and what it meant. They really wanted to understand as much about it as they could. The use of animals was never an issue. They were really very good – no aggressiveness at all.

TL Did you have any media training before you decided to do this or did you go in cold?

SB No – apart from a few 'do's and don'ts' from my press officer on the train, I went in cold – which was both exciting and terrifying. But I was used to talking to people who were non-specialists by doing the schools and general public stuff in Bristol, so I did have some idea of how to put it over.

TL It all sounds really positive. What happened after that – did you get a flurry of interest?

SB When I got the train back home that night after the media briefing, I thought that would be the end of it. But I woke up next day to find that the story has been published in most of the national press – *Times*, *Telegraph*, *Guardian* and even the *Metro*! That morning I got phone calls to do local and national radio interviews, I talked to journalists from Brussels and Rio de Janiero and in the evening I went on BBC News24. It was just a crazy day – but good fun!

TL What about the longer term? Did it all die down?

SB I have not had any negative reactions as a result of publicising my work with animals. One outcome that I hadn't thought about in advance was that people who had been on Roaccutane would try to contact me. I got lots of e-mails from people who said they were so grateful I was doing this work. Usually they were, or had been, on the drug and had always had these feelings that they were getting depressed or had low mood. After hearing about our work they felt vindicated. That was actually quite rewarding and after that first big day it didn't take up too much time.

TL Your work involved mainly behavioural studies on intact mice. What about work that involves more invasive techniques: lesioned animals, animals with implanted electrodes etc. Do you think the public is ready for that?

SB I know that behavioural work on mice is not invasive and therefore in some respects is easier to talk about than other types of animal work. I personally think that, if carefully explained and described, the public will not mind the more invasive studies. I think that once you have made it clear that animal research is very tightly regulated in this country, that the welfare of animals is paramount and that from the scientists' point of view there is nothing to be gained from work on an animal that isn't in the best possible condition, then the public might be prepared to accept the work. But, of course, it is up to the individual scientist to decide what they are comfortable talking about to the public.

TL Do you think it's better to go for a media briefing rather than a press release?

SB Yes I do. I was lucky having made the contact with Fiona Fox already, but given the sensitivity around the topic I felt I had more control by talking directly to the journalists. I think the journalists liked talking to a real person – to get it from the horse's mouth rather than via an impersonal press release. They really wanted to understand what I had done and what it meant.

TL Would you do it again?

SB Definitely! I believe the more scientists feel able to talk about their work with animal research, the more acceptance we're going to get in the public arena for the work that we do. I think we do have a duty to talk about our research and to communicate that to people. After all, our research is publicly funded, be it from research councils or charities. So if we want people to keep on funding research, then we need to let them know what we're doing with their money. You've got to have a good story, or at least a good angle though, one that will appeal to the public because after all, journalists are in the business of selling newspapers rather than promoting science!

Further information and advice about 'going public' can be obtained from the Science Media Centre (http://www.sciencemediacentre.org) and the Research Defence Society (http://www.rds-online.org.uk).

Sudden decline seen in attacks by animal rights extremists

· Far fewer protests at homes of scientists
· Tougher laws and stronger policing seen as factors

The level of activity by animal rights extremists has reached a new low, according to police. Apart from in Oxford, where there is still a vigorous campaign against a new laboratory at the university, attacks at the homes of academic scientists who engage in animal research have ceased.

"What has been very noticeable is quite a sudden and very marked decline in targeting individual researchers around the country in a personal way," said Simon Festing, director of the Research Defence Society, which monitors extremist activity and receives police briefings. "This has really struck me because it has been a major feature of animal rights extremism for 30 years since the Animal Liberation Front was founded in 1976. At any one time there would be many researchers around the country who were being actively targeted and now it has just gone."

For the full story, published in the *Guardian* on 30 June visit: http://www.guardian.co.uk/animalrights/story/0,,2115343,00.html

The dawn of glasnost for research using animals?

A Research Defence Society event held in Birmingham suggested that the activity of extreme animal rights groups may be on the wane

In the past, extremist animal rights groups wreaked havoc with the lives and livelihoods of many associated with animal research in the UK. With a few notable exceptions, such events lead to an understandable reticence amongst those involved in experimentation on animals. The belief that anyone who put their head above the parapet made themselves a target for the extremists, or might be forced into defending animal experimentation instead of explaining their science, has not encouraged a culture of openness. However, there are indications that the tide of opinion is turning and that the public accepts the need for animal experimentation and understands the potential benefits it can bring.

The Research Defence Society (RDS) is currently running a series of regional events to encourage those involved in animal research to be more open. Their Midlands event, hosted by the University of Birmingham in June, was very much an upbeat occasion. During the

course of an afternoon, talks on different aspects of the 'animal question' were given by representatives from the scientific community, the police and the media.

Simon Festing of the RDS and Gordon Mills of NETCU (under the police's anti-terrorism banner) painted a rosy view of the situation in the UK as it stands at the moment. They acknowledged that the extremists do still inspire fear. However, their terrorising tactics have led the public to turn away and to lend their support to campaigns such as the Pro-Test movement or the People's Petition set up by the Coalition for Medical Research. With the exception of Oxford, where protests continue, activity against researchers in the UK is now at an all time low. The Government's standpoint on animal research has also changed drastically. Fuelled partly by concerns of economic damage to the pharmaceutical industry, legislation has been brought in to protect those involved in animal research.

The Open University's Steven Rose, and Sarah Bailey from the University of Bath, both described their positive experience of speaking publicly about their work (see interview with Sarah on p. 37). Neil Yates, Director of Biomedical Services at the University of Nottingham described the successful scheme run in Nottingham whereby members of the University are invited into the animal facility to see for themselves what really goes on. For the media, Alok Jha of the *Guardian*, explained that journalists are intent solely on informing the public about scientific developments. For them, animal research is really a non-issue.

The take home message from this event was that there has been no better and safer time than the present to raise the profile of research and counteract the propaganda and misrepresentation that has been put out by the anti-vivisection movement. The threat from animal rights activists has now receded and those involved in research involving animals should have no fear of being proactive in talking to the public about their work. It remains to be seen whether this message will be translated into a new openness about animal research. More experienced researchers who recall when activism was rife, may still be reluctant to discuss animal research publicly. However, it is to be hoped that younger scientists, who have not experienced extremism first hand, will now have the confidence to be more forthcoming.

Selina Pearson
University of Birmingham

BIOSCIENCES FEDERATION

Use of primates for medical research

You may know that the European Commission/Parliament is currently considering revisions to EU Directive 86/609. This Directive concerns the protection of vertebrate animals used for experimental and other scientific purposes.

What you may not know is that a written declaration on primate research has been tabled.

Written declarations are documents that MEPs are invited to sign. If the total signatures get to 393 the declaration is 'approved' and lodged in parliament: today there are more than 300 signatories and five weeks to go. However, importantly, if the signatories do get to 393 it does not mean that legislation will follow. Nonetheless, the declaration becomes very useful ammunition and, in this case, proposes that all primate research be stopped within a defined time period.

Of course, we would all like to see the use of primates reduced substantially and ultimately eliminated. However, we all know that we remain far from the predictive systems biology that would allow this to happen. In the meantime some primate research is an essential element in our fight against some neurological and other diseases.

Why do I write about this today? The answer is that the Declaration on Primate Research has been signed by many of our UK MEPs. Their postbags are filled by letters from those who want to see animal experiments cease. The BSF, together with other lead organisations, has written to all UK MEPs on this matter and we will go to Brussels in October to speak with some of them. However, private letters are also very important. Have you ever written to an MP on this or any other matter? Sometimes you should and this is one of those occasions. A private letter from you is more effective than your signature alongside many others in a letter from the BSF. And you can be positive and helpful at the same time. All MPs like something to do! Why not suggest that the Commission should provide more funding for research on alternatives and the three Rs more generally. This additional funding might hasten our progress along the route to the predictive systems biology that we need. The approach might encourage substitution of 'timelines' by 'milestones' in the thinking of those UK MEPs who signed the declaration.

If you want to know more, and/or would like to receive contact details for your MEP, please contact Caroline Wallace (cwallace.bsf@physoc.org).

Richard Dyer

The Physiological Society's G L Brown Prize Lectures

Richard Boyd's 2006/2007 lecture tour took in Dundee and Belfast

Dundee

University of Dundee 'old-boy' Richard Boyd returned to the North earlier this year to present his G L Brown Prize Lectures. Richard was at one time a lecturer in the former Department of Physiology at Dundee and many old friends and colleagues, including retired Physiological Society Members Alan Chipperfield and Grant Leslie, were amongst the enthusiastic audience of staff and students from our Colleges of Life Sciences and Medicine. We were all delighted that he had chosen Dundee – a university with a large if now somewhat dispersed cadre of biomedical and clinical physiologists – as one of the lecture venues. The lecture took place in the Sean Connery Boardroom (Room 007 to us locals) of the College of Life Sciences on our main city campus. *(Whilst in name-dropping mode, I must mention that the new College building has been named after Sir James Black, another ex-member of the Department of Physiology).*

After a short introduction on G L Brown himself, Richard delighted us with historical anecdotes about pioneers of epithelial physiology including H H Ussing and Dundee's very own E Waymouth-Reid, highlighting their seminal insights into the mechanisms underlying vectorial transport. Their legacies were then placed into the context of contemporary knowledge and current research into the physiology and pathophysiology of biomembrane transport and epithelial functions. He finished by revealing some novel and unexpected functions of transporters as sensing and signalling molecules which provide information on the external environment to their home cell. Questions encompassed a broad range of scientific (and eventually political) issues including, of course, 'was H H Ussing the greatest 20th century physiologist not to win a Nobel Prize?' (no vote was taken on this issue, although the debate continued long into the evening).

G L Brown (1903-1971). Photograph courtesy of Godfrey Argent Studio

Broader discussion ranged from the suitability of Bahnhof kiosks as physiological equipment suppliers (see Boyd & Ward, *J Physiol* **324,** 411–428) to the admirable qualities of Dundee tap water for rearing amphibians such as *Necturus* and *Xenopus*. The lecture was followed by a short reception where speaker and audience made (or renewed) acquaintances, then a thoroughly pleasant Italian meal (all well within budget, as Richard asked me to point out). Richard stayed in Dundee to visit friends after the lecture and, to quote him verbatim, 'the Glens of Angus were simply a reminder of why the people who stay(ed) in that part of the world (like Waymouth Reid) have a lot going for them!' Haste ye back, Richard.

Peter Taylor
Molecular Physiology, Sir James Black Centre, University of Dundee

Belfast

Richard Boyd delivered The Physiological Society's G L Brown Lecture, *Epithelial physiology: facts, fantasies and fun*, at Queen's University Belfast on 16 February 2007. The South Lecture Theatre at The Medical Biology Centre was packed with undergraduate and postgraduate students as well as academics from different disciplines. Richard gave a fantastic lecture which made us laugh and think deeply about the joys of epithelial physiology. What was wonderful for us was his knowledge of the history of the subject and how he brought it alive and showed that in some ways the old work is as important as our current work. In many ways it was a homecoming for Richard as his parents had met while studying medicine at Queen's.

In addition to his lecture, Richard gave generously of his time and spent the morning at the Medical Biology Centre with members of the Cell and Metabolic Signalling Research Cluster, and then the entire afternoon with members of the Respiratory Research Group at the Institute of Clinical Science. He heard short presentations from PhD and post-doctoral students about their work culturing bronchial and nasal epithelial cells from patients with asthma, COPD and cystic fibrosis. He was particularly interested in our preliminary studies on cystic fibrosis epithelial cells. However, he had something pertinent to say to everybody and he made them feel so special because his questions showed how carefully he had been listening to their work. Our last speaker was a young anaesthetist who talked about his planned work - this research will be much improved after Richard's suggestions.

His visit to the Department of Physiology was finished by a superb dinner together with the wonderful company of his wife who has research connections with the University of Ulster. They were planning on touring Northern Ireland for the rest of the weekend and we hope that they had a lovely time.

Alexander Zholos, Madeleine Ennis
Queen's University Belfast

Molecular Techniques Workshops 1996–2007: an integrated approach to teaching molecular biology to physiologists

April 2007 marked the end of a 10 year programme of Molecular Techniques Workshops (MTW) sponsored by The Physiological Society and the Wellcome Trust. Since 1996, more than 150 post-graduate students, post-doctoral fellows and the odd professor or two have enrolled in these 10 day residential workshops gaining hands-on expertise in how to extract, amplify, characterise, and modify genetic material, and then learning how to apply this knowledge to problems of physiological interest. The workshops have benefited immensely from the vast range of external seminar speakers who have travelled to Cork and Glasgow to share their insight and expertise on almost every area of molecular physiology from *in vitro* and *in silico* characterisation and modification of individual genes, to *in vivo* modification of the genomes of animals and even patients through the use of virus vectors.

Molecular Techniques Workshop organisers 1999–2007 – Stan White (left), Rod Dimaline and Patrick Harrison.

Molecular biology and physiology arguably went their separate ways with the Nobel Prizes in Medicine and Physiology for discoveries concerning the 'Molecular structure of nucleic acids and its significance for information transfer in living material' in 1962 and the 'ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane' in 1963. Despite the intrinsic relationship between the two disciplines, a majority of physiologists had trained in the absence of molecular biology techniques. The Physiological Society made a commitment in the early 1990s to close the gap between the disciplines and ignite a wider interest in the use of molecular techniques by physiologists. The first step was the formation of a Special Interest Group (SIG) in Molecular Physiology which held its first scientific meeting at the University of Oxford (Allen, 1995). This was followed by two further teaching initiatives to train physiologists in molecular techniques. The first was the organisation of one-day teaching symposia to deliver 'Jargon-free molecular biology for physiologists' to a relatively large audience at summer meetings of The Physiological Society (Allen, 1997). The second was the establishment of an annual residential two-week basic training programme in practical and theoretical molecular biology techniques for a much smaller group of research-active physiologists.

The first three workshops were organised by Janet Allen at the University of Glasgow (Allen, 1998). Since 1999, the workshop has been directed by Patrick Harrison, initially at the University of Glasgow and, since 2001, at University College Cork. With invaluable assistance from Rod Dimaline (University of Liverpool) and Stan White (University of Leeds), the workshop has evolved to cover a range of molecular techniques taught in the context of a physiology research project (Harrison, 2004). One key aim of the workshop was to encourage a long-term adoption of molecular techniques by participants. When contacted up to 2 years after their attendance at workshops (de Winter, 2004), many participants indicated that they had adopted a number of the techniques from the workshop into their research. Moreover, attendance at the workshop had allowed participants to 'speak the same language as molecular biologists', facilitating 'sensible discussion of collaborative projects with molecular biologists' and, in some instances, made them 'better integrative physiologists'.

So, after 10 workshops, what next? The workshop has always focused on the delivery of theoretical and hands-on training in molecular techniques to those with very limited previous experience. In the early days, more than 100 applicants applied for the 16 coveted places on the workshops. However, in more recent times, the number of applicants has dropped suggesting that an increasing number of students are gaining theoretical training, and at least some practice, in the techniques from their physiology BSc and PhD programmes. Moreover, the substantial increase in physiology research papers which include molecular techniques (often published in physiology journals) provides further evidence that molecular biology is now a fully integrated part of the discipline of physiology.

Thus, it would appear that the 10 day MTW has succeeded in providing an insight and basic training in a broad range of molecular techniques for students who could not obtain it elsewhere during an era when molecular biology was disconnected from physiology. Now that the two subjects are integrated, and a new generation of students is being taught physiology by physiologists who have a sound grasp and research experience of molecular techniques, the challenge would appear to be to provide more hands-on specialised training in techniques applicable to their particular research programmes. Whatever the future of such training the most profitable use of molecular techniques will arise from discussions

and collaborations with other scientists using such methods; 'Never clone alone' (Allen & Brickman, 1973).

Patrick T Harrison[1]
Stanley J White[2]
Rod Dimaline[3]

[1]Department of Physiology and BioSciences Institute, University College Cork, Ireland
[2]Institute of Membrane & Systems Biology, University of Leeds, Leeds, LS2 9JT, UK
[3]Physiological Laboratory, School of Biomedical Sciences, University of Liverpool, Crown Street, Liverpool L69 3BX, UK.

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The Society's Education Committee is currently exploring the 'fourth' series of Molecular Techniques Workshops . We envisage that the 10 day all encompassing workshop will be replaced with a number of short workshops offered on a mix-and-match basis in locations around the country. Basic theoretical and practical molecular techniques (e.g. DNA/RNA extraction and analysis) will be included, as in the current workshop. We also plan to introduce workshops and include materials on newer technologies such as Microarrays and SiRNA.

It is important that these workshops support the needs of our membership; we will therefore be circulating a questionnaire to find out how you would like these workshops to run, the techniques you'd like covered and, indeed, if you think there is a still a need to run the MTW now that basic molecular biology is integrated into most physiology(-related) degree courses.

Teaching physiology – challenges, successes and rewards

Teaching Special Interest Group co-convenors Judy Harris and Richard Helyer (pictured below planning a new physiology practical class) report on an 'information-gathering' workshop held at King's College London in July for staff responsible for leading and co-ordinating physiology teaching

This workshop, funded by The Physiological Society's Education Committee, enabled representatives from 24 institutions across the UK to discuss the challenges, successes and rewards associated with physiology teaching. We also discussed how The Society in general, and the Teaching SIG in particular, could support members with a keen, and possibly principal, interest in teaching.

A widespread current challenge in teaching is preserving physiology as a distinct discipline in the eyes of undergraduates when there are now so few physiology departments in the UK – only one identified physiology department (Bristol) was represented at the workshop and even that was shortly to merge into a department of physiology and pharmacology! An on-line questionnaire completed by around half of the participating HEIs (Fig. 1) showed that, whereas it is still possible to graduate with a degree in physiology from a number of universities, many more students now graduate with a generalist degree in biomedical sciences.

Another common experience was the dwindling number of staff willing and able to teach systems physiology despite its fundamental importance, not only for physiology undergraduates, but also for a wide range of vocational degrees such as medicine, dentistry, nursing and veterinary science. It was agreed that this is largely due to the recent explosion in molecular physiology combined with a cultural shift in the expectations of staff, many of whom no longer expect to teach outside their research area.

These challenges have been partially resolved in several HEIs by the recruitment of physiology teaching specialists and there was a lively debate on the need to support and reward such staff. Prem Kumar (Society Meetings Secretary) suggested that The Society could consider offering full membership to teaching specialists and encourage them to attend meetings and workshops by providing travel grants and bursaries. The new Themed Meetings – at which teaching-related

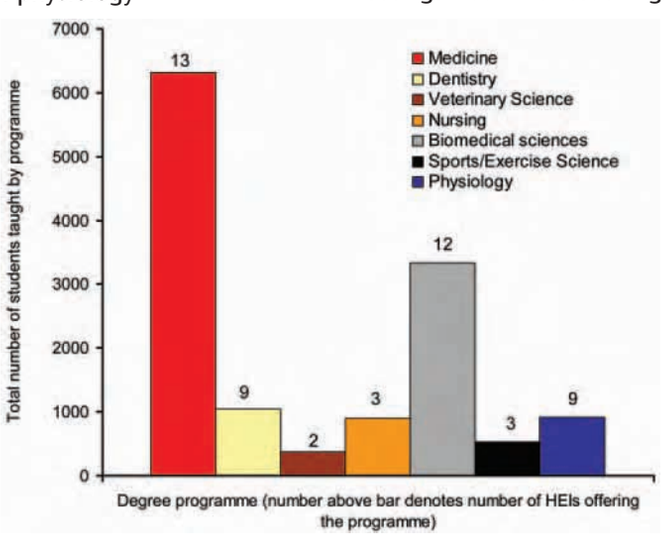


Figure 1. Numbers of undergraduates who receive physiology teaching on various degree programmes (data obtained from 14 HEIs throughout the UK).

posters and oral communications will be welcomed – are intended to provide a forum for disseminating advances in teaching as well as research.

There was widespread support for an additional suggestion from the floor that The Society, possibly with other learned societies, could work with organisations such as HEFCE and the Higher Education Academy to develop criteria for scholarly activity that could be used in relation to career progression/promotion for teaching specialists.

The increasing size and diversity of student cohorts puts pressure on staff to develop innovative and efficient methods of teaching and assessment that engage students without 'dumbing down' the subject. Furthermore, physiology practical teaching has to take due regard for Health & Safety, disability and animal legislation.

Despite these undoubted challenges, it was clear that there is a wealth of expertise, enthusiasm and innovation in physiology teaching that deserves to be shared, celebrated and debated more widely within The Society. Some good practices depend on local resources and/or infrastructure and may therefore be difficult to export to other HEIs but many are 'transferable' activities.

The latter include problem-based and enquiry-based learning; patient-based case studies; skills development modules (e.g. maths, physics, chemistry, writing, research); activities related to the public understanding of science; quizzes/games; field courses; web-based resources; and learning collaborations with schools, businesses and the community. Within the area of assessment there is much good practice in developing grading/marking schemes, assessing practical skills and developing student peer assessment.

Another initiative with great potential value for teachers – flagged by Society Education and Membership Manager, Donna Brown – is the development of a shared resource of web-based physiology teaching materials in collaboration with the American Physiological Society.

As well as the clear potential for Members of The Society to exchange teaching materials and practices amongst ourselves, there was also support for future teaching events to include invited speakers who could address topics such as current changes in the school science curriculum, the school/university interface, learning styles, and educational research approaches that could be applied to physiology.

The workshop was a very useful and enjoyable 'networking' opportunity and threw up several ideas for future events – we will do our best to incorporate them into a lively programme of activities for the Teaching Special Interest Group!

Judy Harris
Richard Helyer
Department of Physiology and Pharmacology, University of Bristol, UK

Teachers turn students for the day ...

... but are they as well behaved as their own students? Jayne Hastings, organiser of the latest Physiological Society supported teachers workshop reveals all

A recent A-level teachers' workshop hosted by the Department of Biomolecular and Sport Sciences at Coventry University drew upon the strengths of lecturers who teach physiology on biological, biomedical, and sport and exercise science degree programmes. The workshop was aimed at those teaching physiology to A-level Biology, PE or Sport Science students by including aspects of cardiovascular and respiratory physiology and metabolism common to both subject areas.

The programme was designed to update the knowledge and practical skills of teachers, provide ideas for teaching physiology in their own classrooms and generally excite interest in the subject area. The laboratory activities were designed to be very 'hands-on' and allowed teachers to use equipment which they may not normally have access to in their school/college, but tutors taking the laboratory sessions did provide suggestions for, and give the opportunity to use, alternative and more accessible equipment when available.

Bodycare® products supply equipment used in physiology and sport science teaching to many educational establishments in this country and we were very pleased that they could support the event, with Spencer Newport joining us for the day. The event was organised in collaboration with The Physiological Society.

After a welcome cuppa on arrival, the teachers had a brief introduction followed by a session on *Careers in physiology* by Rob James. A brief introductory talk then followed to bring the teachers 'up to speed' on the physiology behind each of the laboratory sessions that they would be taking part in during the day. It must be noted that the teachers were very well behaved in the classroom and sat quietly throughout this part of the morning (unlike most of their students I bet), but were eager to get into the laboratory after another cuppa!

The first lab session, lead by Andi Drake, allowed teachers to look at methods to determine metabolic rate and energy expenditure using expired air analysis as well as various procedures for the direct determination of oxygen uptake which included the Douglas bag method and a breath by breath online method. Bodycare's Spencer Newport put a couple of the teachers through their paces on the cycle ergometer whilst demonstrating Fitmate®, a desktop size metabolic system designed by COSMED. This system performs fitness assessments and functional evaluation, including accurate measures of Resting Metabolic Rate (RMR) and oxygen uptake during either sub maximal or maximal oxygen uptake (VO_{2max}) tests.

After a lovely lunch in the University's Riley Lounge, the teachers then went on to look at the cardiovascular system lead by Ray Carson. Teachers used the PowerLab® setup with LabTutor® software to look at the electrocardiogram (ECG). In this lab

Top: Teachers get on their bikes to look at how respiratory volumes change with exercise. **Above**: Experimenting with methods to determine metabolic rate and energy expenditure using expired air analysis.

the teachers identified the major components of the ECG, how they relate to the electrical activity of the heart, and the relationships between the electrical activity of the heart (as recorded in the ECG) and the mechanical activity of the heart (as judged from the heart sounds).

The final lab class was lead by Sadie Mercer with the aim of demonstrating the different volumes that can be measured in lung function testing using spirometers and peak flow meters. This also included looking at how respiratory volumes change (but not the overall capacity) with exercise so meant our teachers were told to 'get on ya bike' one last time during the day.

The day ended with some cold refreshments, welcomed in particular by those that had built up a sweat in the labs, and a brief talk by Irrum Magre, who had joined us for the day from The Physiological Society. Irrum spoke to the teachers about The Society and what it has to offer for teachers, including the Schools and College Associate membership which has recently become available to those who teach physiology.

The feedback from the teachers who attended was very positive, both verbally and via the evaluation forms completed, even from those teachers that we had put through their paces in the lab! This was very pleasing to hear after all the hard work that went into organising and delivering the day. A big thank you to everyone involved.

We are now planning a student workshop for 21 November 2007.

Please contact Irrum Magre (imagre@physoc.org) for more information.

Jayne Hastings
Senior Lecturer in Sport and Exercise Science, Coventry University, UK

Physiology for schools and colleges

Dates for your diary

9–15 September 2007, BA Festival of Science, York
The Physiological Society is organising two events for 6th form students Performance enhancement: the good, the bad and the Olympic gold and The bionic ear show and debate. For details and to register for free tickets:
http://www.physoc.org/education

3–5 January 2008, The Association for Science Education Annual Conference
Biology in the real world. Taking the theory of science and putting it into the context of our everyday lives. Extend your knowledge, talk to experts: an excellent CPD opportunity for teachers and technicians working with 14-19 age group. Further details will be posted on our web site
http://www.physoc.org/education

Can you help?

The Society is looking to develop resources to support the teaching of practical physiology within the A/AS level biology-related curriculum (see Physiology News 67). If you have resources you would like to share with us or an idea you would like to develop contact Donna Brown (dbrown@physoc.org).

The Society has a number of educational grants for its Members to run practical physiology workshops for 6th form students. If you would are interested in running a workshop during 2008 please contact Irrum Magre (imagre@physoc.org).

100 years ago in *J Physiol*

The action of caffeine on the capacity for muscular work

W H R Rivers and H N Webber. August 1907, **36**, 33-47.

Why pick this one? Not because it is an easy read. Like many papers of the era, the absence of schematics detailing experimental design, of summary figures and of statistics makes for heavy going. Also a touch odd to modern eyes is the inclusion of unnecessary, but charming detail:

'In the first two intervals [between series of ergograms] light work was done in connection with tracings (cutting them up, pasting them in a book, etc.); the third interval was passed in light reading and a few biscuits were eaten.'

However, features we would definitely recognise lie buried in the paper. Normalizing data to an initial control value is one; but a second, and the paper's main claim to fame, is its early use of a double blind design employing a control substance, with both experimenter and subject unaware of whether the substance taken was caffeine:

'We took the caffeine in the form of the citrate and the control consisted of a mixture of gentian and citric acid ... it was not till the end of the whole experiment that we acquainted ourselves with the nature of the dose on any given day.'

The doses of caffeine used are modest, roughly equating to peak body water concentrations of 15–30 uM. The authors argue for both central and peripheral fatigue-combatting effects of caffeine, although from a modern standpoint central effects would be assumed likely to dominate. The work also shows marked difference between the two subjects (the authors), who lament their inability to analyse the results statistically. The first reliable approach to small sample statistics actually arrived the following year (1908) in the work of W S Gosset ('student' of *t*-test fame).

A second reason for choosing this paper is that it is one of only two appearances as an author in *J Physiol* of W H R Rivers.

Rivers was a scientist of remarkable range, although in his case somewhat sequentially. Apart from physiologist, which might rank somewhere down the list, the count of Rivers' other professions would include physician, neurologist, psychiatrist, psychoanalyst, psychologist, ethnologist and social anthropologist. Rather startlingly, given this, some of Rivers' biographies describe how he 'fatigued easily' and for much of his life 'rarely worked more than 4 hours a day'! Contemporary academics can only dream of such productivity with such economy of effort.

Rivers has also achieved posthumous fame in literature and on film. He spent WW1 as a military psychiatrist treating shell-shocked officers, including the war poet Siegfried Sassoon. This relationship features in Pat Barker's novel *Regeneration* (1991), and the 1998 film of the same name in which Jonathan Price portrays Rivers.

Rivers' physiological interests were mostly concerned with the senses, and early on he combined an interest in vision with his anthropological and expedition work. Rivers became a Member of The Physiological Society in 1894 (thanks to The Society's scrupulous record-keeping, we even know he was elected on 20 January). His physiologist period seems to have begun when he joined the National Hospital for the Paralysed and Epileptic, meeting London and Cambridge physiological luminaries such as Michael Foster, Schafer, Sherrington and Henry Head. Rivers began teaching sensory physiology in Cambridge in 1893, and was appointed in 1897 to a University lectureship in 'physiological and experimental psychology'. Here he founded the Cambridge psychology laboratory and co-founded the *British Journal of Psychology* (1904). In 1903–7 Rivers was Head's co-investigator in a celebrated experiment in which Head had the one of the sensory nerves in his arm severed and rejoined. The two investigators then plotted the return of sensation over the next several years. Rivers was elected FRS in 1908, around the time he largely ceased physiological work and turned almost entirely to psychological, ethnological and sociological areas.

Rivers died in 1924 of acute intestinal obstruction. Many links to material about him, and some of his writings, can be found in his Wikipedia entry[1].

Austin Elliott

[1]http://en.wikipedia.org/wiki/William_Halse_Rivers_Rivers

The Journal of Physiology
A Publication of The Physiological Society

The Editorial Board

The Journal of Physiology recently welcomed three new Editors, Abigail Fowden (Cambridge, UK), Mark Hargreaves (Melbourne, Australia) and Thomas Voets (Leuven, Belgium) to its Editorial Board.

Abigail Fowden (above, left) is Professor of Perinatal Physiology in the Department of Physiology, Development and Neuroscience at the University of Cambridge. Her research interests are in the regulation of fetal development with particular emphasis on the role of hormones in these processes and on the intrauterine programming of physiological systems. She teaches reproductive biology to medical, veterinary and science students and is a Professorial Fellow of Girton College, Cambridge.

Thomas Voets (above, right) is an associate professor in the Division of Physiology, Department of Molecular Cell Biology at the Katholieke Universiteit Leuven, Belgium. During his PhD in the laboratory of Bernd Nilius (also at KU Leuven, Belgium), he studied cell volume regulation and the gating properties of volume-regulated anion channels. As a postdoc with Erwin Neher (Max Planck Institute for Biophysical Chemistry, Göttingen, Germany) he investigated the mechanisms of large dense-core vesicle exocytosis. Currently, his research focuses on the TRP superfamily, with particular interest in the mechanisms underlying the thermosensitivity of certain TRP channels.

Nine Editors left the Editorial Board at the end of June – George Augustine, Jens Bo Nielsen, Jack L Feldman, Paul L Greenhaff, Peter W Nathanielsz, Ernst Niggli, Bernd Nilius, Quentin J Pittman and Uwe Proske. Their commitment and enthusiasm has been much appreciated by the Officers of *The Journal*.

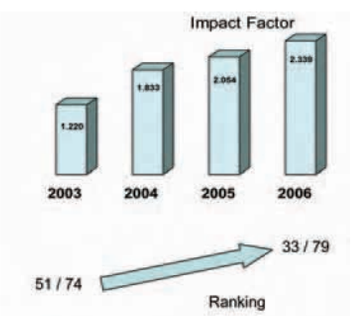
Impact factor

The impact factor for 2006 rose to 4.407 (4.272 in 2005), with a cited half-life of 9.2 years (unchanged from 2005).

Experimental Physiology
Translation & Integration

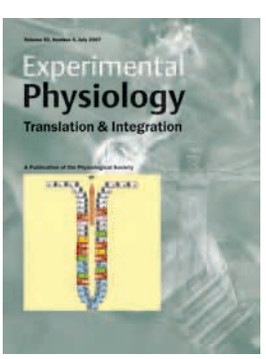
Impact factor

Experimental Physiology's Editorial Board was delighted to see another rise in its impact factor to 2.339 (2.054 In 2005). EP now ranks 33 of 79 physiology journals (a rise from 51/74 in 2003).



Translational review articles

The July issue of *Experimental Physiology* contains the first in a series of translational review articles Contributors to this series have been identified by the Editorial Board as performing outstanding translational research in their field and invited to submit an all encompassing article summarising their work.



Dimaline R. Attack and defence in the gastric epithelium - a delicate balance (92.4, July[1]).
Harridge S. Plasticity of human skeletal muscle: gene expression to *in vivo* function (92.5, September[2]).

Coming soon

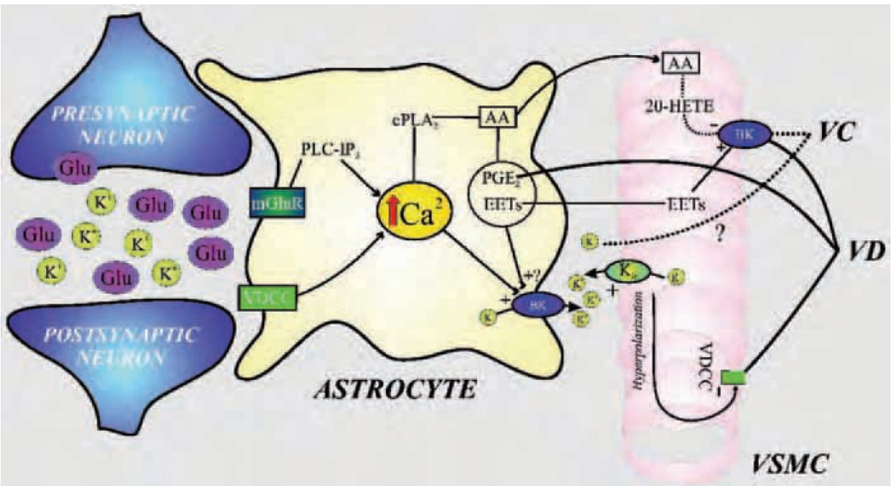
- Garry D. Degenerative medicine and the use of cell based therapies for cardiovascular diseases;
- Pack A. Functional genomic strategies in sleep research;
- Hay B. Translating fetal nutrition into nutrition of the preterm infant.

Symposium Reports from Experimental Biology 2007

Neural-glial-vascular communication in the brain

Over a century ago seminal investigations revealed that brain activity was tightly associated with an increase in blood flow (Mosso, 1880; Roy & Sherrington, 1890), a phenomenon known today as *functional hyperemia*. Since then, enormous efforts have focused on understanding the cellular mechanism underlying functional hyperemia in the brain. It is now clear that rapid increases in blood flow in response to neuronal activation require an exquisite organization involving multiple cell types and signals, a process also referred to as 'neurovascular coupling'. Recent findings have demonstrated the importance of various signals derived from neuronal and glial sources in translating the state of neuronal activity to dynamic alterations in the nearby microcirculation.
The purpose of the *Neural-glial-vascular communication in the brain* symposium[3] was to provide an update on some of the most recent findings addressing the nature of the neurovascular response and the potential mechanisms mediating such orchestrated phenomenon. The

[1]http://ep.physoc.org/content/vol92/issue4/#TRANSLATIONAL_REVIEW
[2]http://ep.physoc.org/content/vol92/issue5/#TRANSLATIONAL_REVIEW
[3]http://ep.physoc.org/content/vol92/issue4/#SYMPOSIUM_REPORTS
[4]http://ep.physoc.org/content/vol92/issue5/#SYMPOSIUM_REPORTS



four reports summarize the topics addressed by the speakers during the symposium. Eric Newman discussed the involvement of K^+ siphoning, metabolites of the arachidonic acid pathway and nitric oxide in the signaling mechanisms underlying neurovascular coupling in the retina (Metea & Newman, 2007). Jessica Filosa addressed current evidence supporting a role for K^+ signalling between astrocytic endfeet and vascular smooth muscle cells and described the changes in intracellular Ca^{2+} that occur in both cell types during vascular responses in the brain microcirculation (Filosa & Blanco, 2007). Dale Pelligrino presented new findings addressing the importance of purinergic mechanisms involving ATP release and hydrolysis, with emphasis on the signaling events underlying the communication between the glial limitans and pial arterioles (Xu and Pelligrino, 2007). Finally, Jeffrey Iliff provided evidence for the expression of a P450 epoxygenase isoform (CYP 2C11) and of soluble epoxide hydrolase in extrinsic parasympathetic and sensory vasodilatory nerve fibers contacting and proposed a novel role for P450 eicosanoids in the neurovascular control of the cerebral circulation (Iliff *et al*. 2007).

Altogether, these reports add new impetus to this exciting area of research and highlight the complexity of the neurovascular response in the brain.

Jessica Filosa

Neuroimmune interactions

The articles to be published in the September issue of *Experimental Physiology*[4] summarize information regarding the integration between the immune, endocrine and central nervous systems, an interaction discovered by Hans Selye in the 1930s. During the last decade the importance of neuroimmune regulation has been recognized, and this recognition has stimulated research in this area. This interaction assures that immune and neuroendocrine responses are in harmony with other physiological functions, in order to maintain homeostasis and health. Neuroimmune interactions provide host defense against infection, injury, cancer, and also psychiatric disorders. Neuroimmunoregulation also contributes to intestinal physiology, secretory immune function, conception and the transfer of immunity to offsprings. It also affects sleep and recovery from diseases. During acute illness these interactions are responsible for the profound neuroendocrine and metabolic changes that play a key role in health recovery. The 'cross-talk' between the neuroendocrine and immune systems is accepted. This crosstalk involves common ligands and receptors being used by both systems, allowing a physiological communication circuitry to play a relevant role in homeostasis. These invited articles provide a review of current investigations regarding this crosstalk – in particular, the neuroimmunendocrine interactions in health and disease. The articles by Eduardo Artz (Department of Physiology and Molecular Biology, School of Sciences, University of Buenos Aires, Argentina), Wilson Savino (Oswaldo Cruz Institute, Rio de Janeiro, Brazil) and Julio Licinio (Department of Psychiatry, University of Miami)cover different investigative approaches using high-throughout technologies such as molecular induction or repression of gene transcription, genome wide scan, genotyping, microarray expression, proteomics and metabolomics.

These three articles demonstrate without any doubt that neuro-immunendocrine interactions are taking place at central level such as brain and pituitary gland, and in the peripheral organs such as thymus and lymph nodes.

The knowledge of immuno-regulation failed to produce practical solutions to treating human diseases involving autoimmune or chronic inflammatory diseases and cancer. A reason for this failure is probably that the immunoregulatory pathways are subject to neuroendocrine regulation. Therefore, it is necessary to study the role of hormones and neurotransmitters in the immuno-regulatory pathways. Also, it is very important to study the participation of cytokines in the normal and pathological functioning of the neuroendocrine system. These studies promise a better understanding of the role of the immune/neuroendocrine systems in health and may lead to elucidate the fundamental alterations in diseases, which may lie in the neuroimmun-endocrine regulation. Only after understanding the interactions between the immune and neuroendocrine systems we can develop rational approaches for the treatment of inflammatory diseases, cancer and psychiatric disorders.

Valerie Rettori

Coming soon

Physiological genomics: bench to bedside. Reports form M Dwinnel, G Semenza, N Lee and A Kwitek (92.6).

Edward Joseph Conway

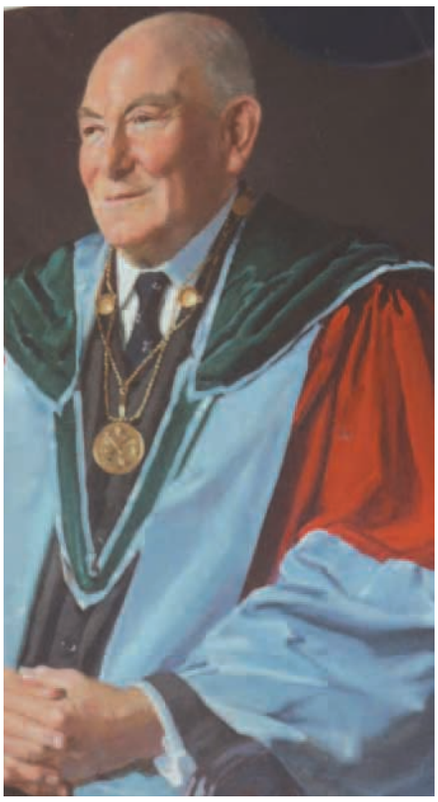
1894–1968

The following is a summary of an address given by Richard Keynes FRS (Emeritus Professor of Physiology at the University of Cambridge) to the Royal Irish Academy in Dublin on 12 December 1994 to celebrate the centenary of the birth of Edward Conway (formerly at the Physiology Department, University College Dublin).

'Conway was born and went to school in Nenagh, North Tipperary. It was in that pleasant countryside that he acquired his lifelong passion for fly-fishing and I have noted with interest on looking at the map that it is not far from Foynes and Limerick and Adare, where on one of my few previous visits to Ireland I had the involuntary, but nevertheless very pleasurable experience, in 1944 of getting stuck for a week because of excessive head winds, when I was supposed to be on my way across the Atlantic in one of the old Boeing Clipper flying boats. After four wartime years of rationing, the excellence of the food and cellar at the hotel at Adare was memorable, and had the marooned passengers had Conway to give us his expert advice on our choice of whisky we might have enjoyed ourselves even more.

'Conway went on to Blackrock College and thence in 1912 to University College. He graduated in medicine in 1921, but never did any house appointments, nor did he ever practice, joining the staff of the Physiology Department under Professor James O'Connor until 1932 when he became the first holder of the Professorship in Biochemistry and Pharmacology at University College.'

Keynes dealt firstly with Conway's earliest research on the structural relations in kidneys from a wide range of terrestrial mammals with 'special emphasis on a mathematical



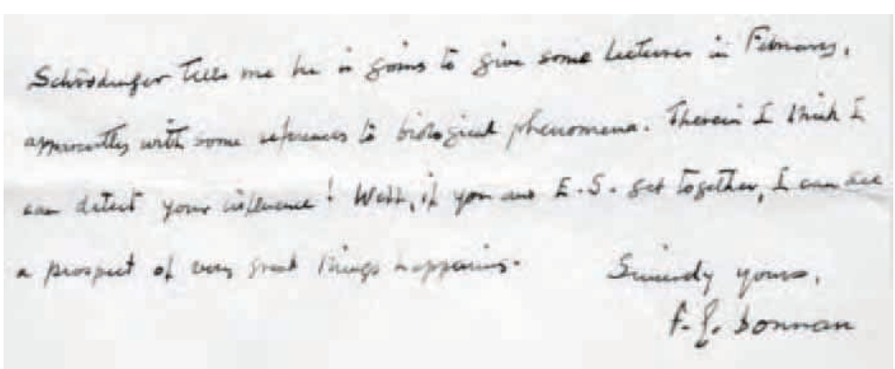
Edward Conway (above) and a sample of the correspondence between Donnan and Conway (Fig. 1, below).

analytical and rigorously quantitative treatment that characterised virtually all his papers'. The first phase of the research from 1921 to 1937 was concerned with the localisation of function in the renal tubule, the important outcome of which was his invention of the 'Conway Unit' and microdiffusion analysis of volatile substances at atmospheric pressure. The unit consisted of a 3 inch glass or porcelain dish containing two concentric chambers whose circular dividing wall was slightly lower than the outer boundary wall. The sample of blood or other fluid to be analysed was placed on one side of the outer compartment and a reagent to release a volatile component from it on the other; an absorbent was placed in the middle compartment. After sealing the dish with a greased cover, it was gently rocked to mix the reagents, and equilibrium with the central measuring compartment was quickly reached.

'Conway's original purpose was the estimation of blood ammonia which was released by the addition of alkali to the blood, and absorbed by a standard acid which could then be back-titrated.' The technique was adapted for estimation of blood urea, oxygen capacity, carbon dioxide, glucose and chloride.

'It continued to give valuable service for many years, until it was displaced by more sophisticated and more expensive techniques. If you wanted to measure blood bicarbonate at 15,000 ft in the Andes one would still have to use a Conway Unit.'

Returning from Gustav Embden's laboratory in Frankfurt, Conway carried out what was perhaps his most important research on the application of the double-Donnan equilibrium to the distribution of monovalent ions in isolated frog skeletal muscles [Boyle PJ & Conway EJ (1941). Potassium accumulation in muscle and associated changes. *J Physiol* **100**, 1–63]. The work was based on a theory of the Belfast physical chemist Frederick Donnan to explain the swelling of gels due to fixed charges. At the time Donnan


Schrödinger tells me he is going to give some lectures in February, apparently with some reference to biological phenomena. Therein I think I can detect your influence! Well, if you and E.S. get together, I can see a prospect of very great things happening.

Sincerely yours,
F.G. Donnan

lived in London, and a lively correspondence passed between the two scientists, a sample of which is shown in Fig. 1.

Conway's daughter, Dorothy, kindly made available to us Donnan's letters to Conway in which he indicated the limitations of his original theory to which Conway replied in letters obtained by me from archives at UCL. Here he outlined the double Donnan equilibrium with the virtual exclusion of sodium from within the fibres coupled with fixed intracellular anionic charge. Keynes illustrated his talk with these letters as well as those carried by *Nature* (4 April 1942, p. 383). By adding potassium chloride to physiological saline bathing isolated muscles of frog, Conway showed that the membranes were permeable to chloride and that at equilibrium the product of molar concentration of these permeable ions within the fibres was equal to that of bathing fluid.

Richard Keynes also reviewed Conway's work on the evolution of the ocean, published in the Proceedings of the Royal Irish Academy, illustrating the breadth of his interests. The great grandson of Charles Darwin showed how Conway demolished Macallum's over-simplification of evolution with respect to salinity of oceans and blood.

Finally, Keynes reviewed Conway's redox pump theory which originally sought to explain gastric acid secretion, using as a model acid secretion by yeast fermenting in the presence of potassium chloride, but perhaps unwisely extended to the active transport of other cations.

Sadly, Conway didn't see its relevance to the synthesis of ATP for which Peter Mitchell reaped the benefit, resulting in his Nobel Prize in Physiology in 1988.

Roderick P Kernan
Dublin, Republic of Ireland

Noticeboard

PHYSIOLOGICAL SOCIETY MEETINGS & INTERNATIONAL WORKSHOPS

2007

Manchester, UK
5–6 September
Focused Meeting *Cardiac electrophysiology: with a special celebration of the centenary of the discovery of the sinoatrial and atrioventricular nodes.*

Bratislava, Slovakia
11–14 September
Joint Meeting of The Physiological Society, the Slovakian Physiological Society and FEPS.

Yaremche, Ukraine
19–23 September
International Workshop *Molecular physiology of membrane transport and cell excitability.*

Bristol, UK
17–18 December
Focused Meeting *Renal cortex: physiological basis of glomerular and tubular diseases.*

2008

Leeds, UK
17–18 March (to be confirmed)
Cardiac & Respiratory Physiology Themed Meeting with a Focused Symposium on *Determining control of the cardiovascular system in health and disease: from brain to blood vessel*.

Cambridge, UK
14–16 July
Main Annual Meeting.

Oxford, UK
9–11 September
Metabolism and endocrinology Themed meeting with a Focused Symposiun on *Orchestration of metabolism in health and disease.*

Beijing, China
20–22 October
Joint International Meeting of the Chinese Association for Physiological Sciences, the Canadian Physiological Society, the Australian Physiological Society, the American Physiological Society and The Physiological Society.

King's College London, UK
December
Vascular and smooth muscle physiology Themed Meeting with a Focused Symposium on *Vascular responses to mechanical stress: cellular cross-talk and integration*.

For full details of Society Meetings and International Workshops visit http://www.physoc.org/meetings.

The Benevolent Fund

Every year, at The Society's Main Meeting, the Benevolent Fund puts on a raffle. This year at Glasgow Life Sciences, £136 was raised with all proceeds going directly to the Fund. The winner of the raffle was Alasdair Gibb (University College London). The raffle prize, a case of wine worth £100, was kindly donated by The Physiological Society.

The Trustees of the Benevolent Fund would like to thank everyone who bought a raffle ticket, as well as all those who have contributed, and continue to contribute, to the Fund. If you are interested in donating, please contact Elfa Wilmot at The Physiological Society's London office or visit The Society's web site for more information (www.physoc.org/benfund).

The Benevolent Fund exists to help anyone who is, or has been employed in the field of physiology and pharmacology; they don't have to be Members or former Members of The Society. The Fund helps by providing grants in aid of funeral expenses and emergency travel, medical costs, childcare arrangements, relocation costs and other unexpected bills. If you know of someone who the Benevolent Fund might be able to help, then please contact the Chair of the Trustees, David A Brown, at University College London (d.a.brown@ucl.ac.uk), or Elfa Wilmot (ewilmot@physoc.org)

Conflicts of interest and science education

Two meetings in the last few months might be of wider interest to our Members – one on conflicts of interest and the other on science education. I also attended an interesting discussion on *Science and religion* in the hope that something would be said about topics close to our research hearts such as embryos/stem cells. Unfortunately, it concentrated on Intelligent Design (ID) versus Darwinism, so I haven't written that one up in detail. However, I was interested to note in my discussions with the proponents of ID (and yes, I was terrified, I think I would personally have found it easier sitting next to animal rights activists – at least I know what to say to them), that the ID debates seem somewhat different to the creationist debates of the 19th Century. I was surprised to find that they didn't seem to dispute natural selection or the mutability of species (which I would have felt qualified to argue about) as affecting populations of creatures in the current biosphere, but were unprepared to believe that complex biological systems could have evolved under their own steam from humble and ultimately originally inorganic origins. I was also interested to observe that the scientific proponents of ID present came from engineering backgrounds, people who were professionally used to having to actively engineer things to create artefacts. Needless to say they were given a hard time by all the life scientists present. So I was left thinking that as a bioscience community we really need to explain in simple, understandable terms to the general public (that ID is currently trying to influence) the mechanisms of how complex organic life forms can arise without active intervention.

Conflicts of interest – does money influence scientific publication? (15 January)

Our President, Ole Petersen, came with me to this session. The speakers were Richard Smith (United Health Europe), Sir Iain Chalmers (Editor, James Lind Library), and Clive Wilson (Strathclyde University and Royal Pharmaceutical Society of Great Britain). Some very interesting key points came up in the presentations and subsequent discussion. The session defined a conflict of interest as a set of conditions in which professional judgement concerning a primary interest (such as patients'

welfare or the validity of research) tends to be unduly influenced by a secondary interest such as financial gain. There was concern that conflicts of interest could be pervasive in healthcare, bur rarely declared.

Smith gave an interesting example of where funding of projects looking at whether contraceptive pills led to an increased risk of clotting, seemed to have had an impact on the research findings. Of a sample of articles submitted to the *British Medical Journal*, every one funded by industry found that there was no link, and every one funded by public money found there was. Other studies have found similar correlations in other areas such as papers on tobacco. Declarations of interests is one strategy to combat this, but even with the best of personal intentions, authors can have imperfect insight into their own potential conflicts of interests. Many doctors fail to declare a conflict because they are confident it has not caused them to behave in a different way. Double-blind randomised trails are important, not because researchers are consciously dishonest, but because bias is pervasive and unconscious. The *BMJ* has found that in declarations you have to ask very specific questions to help draw pertinent information out on, for example, symposium expenses, stockholding, etc. An issue is that although it is now common to ask authors of potential journal articles to declare their interests, less attention is often paid to checking out the editors and editorial boards. He summed up by saying that we need clear disclosure systems at all levels in the publication process, from the authors, through the editorial boards to the presidents of the learned societies connected with the journals.

Chalmers talked about how conflicts of interest can arise in clinical science. Here industry can have a big influence, even down to the level of design of studies that affect reports sent to agencies in pre-licensing submissions. It is often left to industry to fund relevant studies, more public funding is needed to support research instead of this to avoid some of the biases, e.g. under-reporting of potential side effects of new treatments, and to open up wider scientific debate on potentially problematic issues. The Italian drug regulatory agency has taken this on board and now provides funding for independent clinical evaluations, the UK should take heed of this. More transparency is generally needed, for example the creation of a register of clinical trials.

Wilson noted that the downside of the entrepreneurial spirit can be selfishness. The danger in the pharmaceutical industry is that in the worst cases the patient's interests are not necessarily put ahead of the shareholder. Cases of bad practice that have been uncovered cast doubt on a purely market-led approach. He highlighted the rise of the complementary/alternative medicine sector, pointing out that from the public's point of view medicine might have reached a fork in its development with traditional, evidence based, western medicine on the one hand and complementary/alternative medicine on the other. New conflicts of interest issues can be expected to arise in smaller companies working on the fringes of medicine. In his view, medical publications have a duty of trust in providing reliable information to the public. Perhaps we will see new forms of clinical trials appearing to address this need?

In the ensuing discussion it was generally felt that increased regulation of clinical trials would be a good idea, and that the UK would benefit from copying the Italians to create an independent public body whose findings the public could trust. Industry for its own long term survival needed to address loss of public confidence arising from perceived conflicts of interest and put its house in order. Complacency in industry will not be tolerated, with the mass media keen to expose conflicts of interest when they arise. Ole stressed that the biggest problem was the interpretation of results, effective peer review processes are vital in this, but are increasingly under threat from many quarters

including from changes in the RAE. We need to look at bolstering peer review and rewarding it so that people are motivated to engage in it. Our Society's journal publisher, Blackwell Publishing, also got a positive mention in the discussion, with editors clearly separated from the financial side of the journals, and published guidelines on transparency.

Science education for the 21st century (21 May)

The speakers were Robin Millar (Salters Professor of Science Education, University of York), Derek Bell (Chief Executive, Association for Science Education), and David Perks (Head of Physics, Graveney School, Tooting).

Robin Millar noted that the proportion of students choosing to study science beyond GCSE is falling. A House of Lords Select Committee report has emphasised that the role of science education in schools has a dual mandate, it must not only be to prepare students wishing to study science at university, but also to develop general science literacy skills in the population. The UK needs a population that can understand scientific issues, the MMR scare is a good example where failure to achieve this led to many parents refusing to vaccinate their children on the basis of perceived risk. However, the dual mandate is difficult to get to work in practice, students tend to see much of the science curriculum as being irrelevant to their daily needs. Teaching academic science to the whole population often doesn't work. Under the dual mandate, a single science course for everybody is an unsatisfactory compromise, different sorts of science courses are needed for students with differing aspirations. The new GCSE science syllabus has attempted to provide this. Although still too early to see if it works, there has been some good feedback from teachers on how prepared students are for A-Level. Robin finished by saying that the 21st century science syllabus needs to become more creative in developing practical skills, with more access to ICT, etc. The choice structure also needs to allow students to pick up science at any stage in order to encourage older students to pick up science again.

Derek Bell emphasised the vital role of teachers. Debates on the parlous state of education are anything but new, a 19th century Royal Commission described science education in schools as 'extremely unsatisfactory'. From the ASE's point of view, all students should experience a broad, relevant science curriculum which puts the understanding of science and its applications in a social context. Students should experience a variety of teaching and learning approaches including practicals. Teachers are the essential resource in this, but often struggle to juggle the curriculum, assessments, admin, etc. Facilities are also often inadequate – there is an urgent need to invest in modern labs. Teachers need to be qualified for the specialties they teach. Having a relevant degree doesn't always indicate breadth of knowledge. We need to think about how to prepare teachers to teach the curriculum. Experienced teachers need CPD to keep them up to date. A very big issue is that we may not be able to hold onto the teachers we've got, surveys show a lot of professional dissatisfaction. Teaching to the test has been a concern with many people now perceiving assessment as being part of the problem, but if approached properly it can raise motivation and standards. Students' initial experiences are very important in getting them interested in science, it needs to connect to their personal circumstances, and include looking at exciting new discoveries, potential applications and ethics. We need to get away from 'can't do that, it's not on the curriculum' attitudes and engage with events in the real world such as what students and their families see on the news. He concluded by saying that there have been so many curriculum changes that we need to stick with it now to give it a chance to work. Constantly chopping and changing brings many problems of its own.

David Perks then gave us a very thought provoking view from the teaching coal face, challenging some of the assumptions of the other speakers. The dual mandate can't be addressed in the same curriculum. We need to see science education as being worthwhile in its own terms, there is a danger of science education in schools becoming politicised as different lobbies try to give it a sense of purpose. There is a particular danger of education being used to address social issues where young people are perceived to be making the 'wrong choice'. For example the Government is currently struggling with how to 'sell' nuclear power to the general population, promoting scientific literacy in schools is supposed to address this. It could also be a problem in terms of the age group being addressed. Teachers are now encouraged to avoid taking a particular line on any debate, but 14 year olds often prefer clear direction. Surveys of student attitudes show that their confidence in scientists drops after scientific literacy debates, for example discussions on animal research or GM foods can put kids off careers in science based industries. We must be very careful about raising ethical issues in classrooms and leaving them unresolved, as students will be left with a negative perception of science. David felt that traditional models of teaching science can provide a better solution, can inspire students more even if they don't fully understand it, and can be many students only experience of academic science. It is difficult to teach scientific method to students through presentations, students can only learn by doing. Students love to do practicals but get less chance to do them these days.

In the subsequent discussion I raised the issue of the importance of practical training in schools, and our Society's concern at its apparent decline. Practical training is needed to initially enthuse students, to reinforce learning (much social science research has highlighted the importance of learning by doing), and to feed through to the practical skills needed by academia and industry. I got a lot of support for this. One discussant from a Small and Medium Sized Enterprise (SME)) said that practical skills are vital for SMEs which can't fall back on in-house training resources like large companies. Someone from the Teachers Science Network in Norwich said that practical training is essential, we need properly equipped labs. They have received a lot of feedback from students saying that they want more practicals. Baroness Joan Walmsley (Lib Dem), a former biology teacher, said that she liked the idea of teaching science for science sake, and the importance of practicals in helping them learn by doing. Another discussant raised the interesting issue of the need to inspire students at primary school, get them interested in science before the hormones kick in at puberty and they become interested in other things.

I was lucky enough to be able to continue the discussion with David on animal research, when he made a subsequent presentation at a meeting of the Coalition for Medical Progress. He stressed that speakers in schools were useful, but not if they came to try to give a 'balanced' view, leaving ethical issues unresolved. It is better for speakers to

nail their colours to the mast, and make a case for whatever lobby they represent as students find it easier to engage with this. I was pleased to note from this that our new Society DVD, *Animals in research: make up your own mind,* which focuses strongly on the case for biomedical research, does seem to fit the bill here. Please contact me if you'd like a copy (ebell@physoc.org).

Liz Bell

Joint PhySoc/BPS medical training initiative

The Physiological Society's Executive Committee has paid considerable thought to the issue of how our discipline is represented in medical training, and identified this area for action at its 'Prioritisation' meeting last October. Ole Petersen and I then attended a lively Hot Topics meeting of physiology and pharmacology Heads of Departments (HoDs) in Manchester (28–29 March) which focused on medical training issues. The HoDs meeting asked us to set up a joint Physiological Society/British Pharmacological Society Working Group to discuss and potentially make recommendations about the future content of physiology and pharmacology in the medical curriculum. We've now set up this Working Group, chaired by Ole, with the following members: Paul Bromley, Austin Elliott, John Lee, Eugene Lloyd, Amanda Mackenzie, Simon Maxwell, Ian McGrath, Richard Naftalin, Clive Orchard, Peter Roberts, Dafydd Walters and Jeremy Ward.

HoDs were concerned that the teaching of scientific principles may need to be reinforced in medical training. It was felt that the teaching of physiology and pharmacology might have become a particular issue, because understanding of physiological principles is important for medical diagnosis and insight into disease processes, and pharmacological knowledge is vital to safe and effective prescribing. Doctors are also becoming increasingly under pressure because they are having to assimilate the rapid expansion in scientific and medical knowledge. In addition patients are becoming, quite correctly, better informed about their illnesses and the risk of medical litigation is increasing.

In the first phase of the Group's work, the two societies will be looking at defining a core curriculum in physiological principles to support the publication already produced in this area by the BPS (*Teaching safe and effective prescribing in UK medical schools: a core curriculum for tomorrow's doctors*) by Simon Maxwell and Tom Walley in 2003. It is hoped that this will help in the design of courses in medical, dental, nursing and other health sector training schools, and that we might eventually follow this up by looking at how our societies can help develop parallel systems of assessment. There may even eventually be a niche for new professional qualifications in medical physiology and pharmacology, which could be attractive for qualified medical professionals to pursue through continuing professional development. We will be kicking off this work with a short survey of schools over this summer to try to identify particular needs.

If you'd like to contribute to the work of this Group, please contact me (ebell@physoc.org).

Liz Bell

Annual General Meeting

The Annual General Meeting of The Physiological Society took place in Glasgow on 11 July.

Elections

This year saw the introduction of online voting for the Council election. This proved to be very popular, with more than double the number of votes cast compared to last year. Godfrey Smith (University of Glasgow) and John Winpenny (University of East Anglia) have been elected to Council. Two new Affiliate representatives have been appointed, Jane Cleal (University of Southampton) and Patrick Howorth (University of Bristol).

Doug Corfield, Sarah Hall, Patrick Harrison, Sergey Smirnov and Keith Thornbury have retired from Council and Patricia de Winter has retired as an Affiliate representative. The Society is extremely grateful for all their contributions.

A full list of Council members for 2007–2008 appears above right.

The Physiological Society Council 2007–2008

Trustees

David Eisner (International Secretary, University of Manchester)
Prem Kumar (Meetings Secretary, University of Birmingham)
William Large (Editor-in-Chief, *The Journal of Physiology*, St George's University of London)
Graham McGeown (Treasurer, Queen's University Belfast)
Ian McGrath (Chairman of the Executive Committee, University of Glasgow)
Clive Orchard (Vice-Chairman of the Executive Committee, University of Bristol)
Ole Petersen (President, University of Liverpool)

Jonathan Ashmore (University College London)
Valerie Gladwell (University of Essex)
Paul Greenhaff (University Nottingham)
John Hanrahan (McGill University)
Anne King (University of Leeds)
Stafford Lightman (University of Bristol)
Christof Schwiening (University of Cambridge)
Godfrey Smith (University of Glasgow)
David Sugden (King's College London)
Alexei Tepikin (University of Liverpool)
Teresa Tiffert (University of Cambridge)
John Winpenny (University of East Anglia)
David Wyllie (University of Edinburgh)

Affiliate representatives

Jane Cleal (University of Southampton)
Patrick Howorth (University of Bristol)

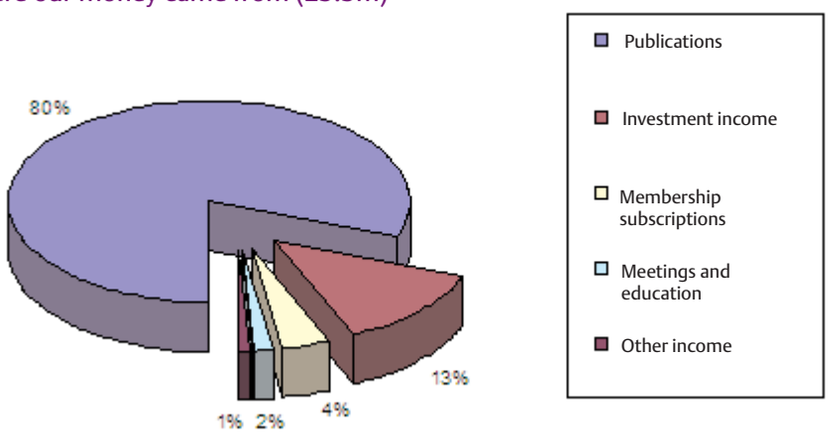
K Michael Spyer (University College London) was appointed an Honorary Member.

Membership rates

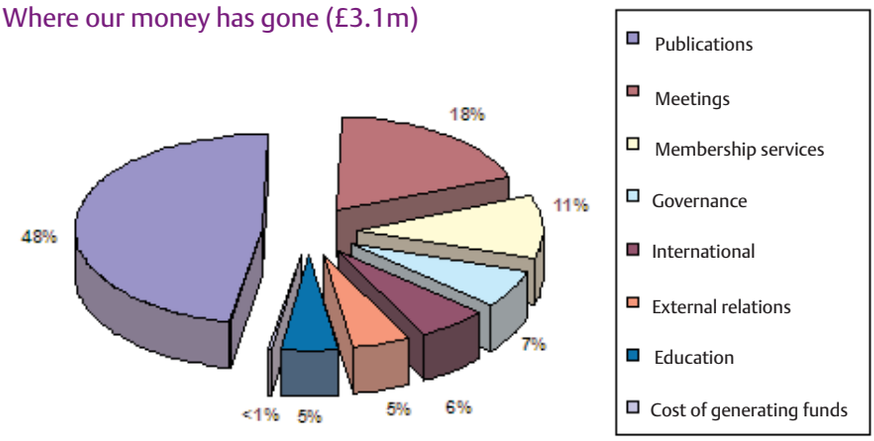
Basic embership rates for Ordinary and Affiliate Members will remain unchanged in 2008. There will be a 5% increase for those Members requiring hard copies of T*he Journal of Physiology* or *Experimental Physiology*. Trial rates will apply to new membership categories – Associate (£45), School and College Associate (£15) and Undergraduate Associate (£15).

Subscriptions are due on 1 January (Ordinary Member) and 1 September (Affiliate). For all new Members who joined on or after 1 January 2007, subscriptions will run on for 12 months from the month of acceptance.

Where our money came from (£3.3m)



Where our money has gone (£3.1m)



For full details visit http://www.physoc.org/membership

2006 Annual Report and Accounts

The 2006 Annual Report and Accounts were approved by the Trustees on 17 May 2007 and subsequently laid before the Members of The Society at the Annual General Meeting. The report is now fully compliant with the new Charity Commission reporting requirements. We have created a document that, I am sure you will agree, is rather more professional and user-friendly than in previous years.

All Members were sent an Annual Report incorporating summary financial statements. The full statements, as filed with Companies House and the Charity Commission, can be found at http://www.physoc.org/downloadfiles/AR2006.pdf.

Summary of accounts

The Society's income remained constant in 2006 at £3.3m (2005: £3.3m). However, expenditure increased by £0.1m to £3.1m (2005: £3.0m) and, as a result, net incoming resources fell by £0.1m to £0.2m (2005: £0.3m). Thanks to the good performance of our investments in 2006, The Society's reserves increased during the year by £1.2m.

Key points

Income

- Journal income is stabilising but the real surplus is falling because of inflationary effects;
- membership income diminished due to free Ordinary Retired subscriptions (subscriptions also frozen in 2008);
- investment income will be reinvested from the middle of 2007 to build up the reserves. These can supplement Society income in future years.

Costs

- Major exceptional items in year: rebranding (£43k) and web project (£85k);
- notable savings were made in direct costs of publishing due to the Blackwell Publishing Singapore operation;
- there was a 3.5% increase in total staff costs;

Balance sheet

- Investments (fund and property) doing well; the capital value growing by £464k and £510k respectively;
- cash balances were high at year-end. This was mostly to do with the timing of a VAT payment collected in December 2006 and paid to HMRC in January 2007.

The Benevolent Fund of The Physiological Society – 2006 financial statements

As at 31 December 2006, the net assets of the Fund were £29,314 (2005: £30,004), a fall of £690. Although income exceeded expenditure by £484, the fund saw a large drop (£1,174) in the value of its COIF Investment Fund (formerly the Charities Official Investment Fund).

Income

Three new annual standing orders for regular giving were received in the year. £1,874 was received in donations and regular giving (2005: £1,505) during the year and income from raffles was £495 (2005: £330). Interest fell by £421 although this was due to a book-keeping correction in 2005. The COIF interest yield is between 5.3% and 5.6%.

Expenditure

Two grants totalling £3,000 (2005: £5,050) were awarded in 2006. School-age children in families of current and recent beneficiaries were sent book tokens or Marks & Spencer vouchers worth £200 in total (2005: £225) for Christmas 2006. Applications for assistance are sporadic and the Fund has no predictable future liabilities or commitments.

The financial position of the Fund is reasonable. The performance of the COIF Fund is a cause for concern and alternatives will be considered in 2007.

Please contact me if you have any questions about the reports in general or the accounts in particular.

C R Early
Finance Manager

A mouse speaks: 'Schedule 1 so lacks panache'

Last week I had a dream. In the dream I took some hallucinogenic drugs. And I took them at work in the university mouse-house.

There is a logical reason why I confined my altered state of consciousness to work. I would like you to think it was because I am a responsible law-abiding adult, and this applies to my dreaming self too. I suspect, however, that my subconscious thinks nobody notices when you are hallucinating in a university neuroscience department. You wouldn't stand out, let's put it that way.

In the dream I used my newly enhanced cognitive state to begin a serious philosophical conversation with a transgenic mouse.

'I don't understand the regulations relating to the euthanasia of mice', I said. ' Neither do I', said the mouse, 'If I had to do all that paperwork every time I ate a beetle I'd be a basket case. And apart from that, the current methods are so boring – no theatrical finesse at all. When I go, I want to go with a bit of style. A friend of mine feigned death and escaped from the freezer last week - which is a pretty neat trick, but he said his near death experience was a bit boring. It's cold in the freezer and when you shut the lid the light goes off. Personally I want spotlights - a bit of spectacle.'

The conversation carried on for a while, until my 5-HT receptors returned to normal (a process which surprisingly rendered me unable to communicate effectively with or read the mind of my furry rodent friend). I then wrote to the Home Office inspector asking for a number of amendments to my animal licence:

' Dear Home Office Inspector,
Yesterday, for scientific purposes only, I took some LSD. The ensuing expansion of my consciousness has given me a number of unique insights into the inner workings of the mouse mind. Following an extended philosophical discussion, a talking mouse and I have come to a unique inter-species agreement. We are in clear accord that the current legal methods of killing mice in the lab are boring and lack a certain "*je ne sais quoi*". We therefore wish to suggest an alternative Schedule 1 method that we would like added to my animal licence. We feel that this technique would bring a certain extra something to scientific research and have the potential to engage bored scientists, sentient mice and members of the public in a whole new philosophical debate about the nature of a good, or at least purposeful, death.

The method, in its essentials, is to throw the mouse into a pit of vipers. This was a favoured liberal alternative to prison in early medieval times, and was notably employed by King Einar of Northumberland to dispose of a troublesome Danish relative, King Ragnar.

I suspect that the Home Office would have had reservations about the method in its original historical use for human subjects. While the vipers are nibbling the ankles of their intended victims they could get trodden on; this is obviously unacceptable from an animal welfare perspective. Using a pit of vipers to dispose of mice avoids these concerns, however. The mice are no threat to the vipers; mice are despatched; vipers are fed.

Pragmatically, I could see this method raising a number of minor legal and technical problems. The pit itself might need special Home Office approval, and there could be problems if a confused escapee snake began wandering around the lab, overexciting the Health and Safety people. The other problem concerns organ retrieval. For our research, mice are often killed and their organs harvested for histology and other experimental purposes. We may have problems with insurance and staff recruitment if we ask technicians or PhD students to retrieve tissue samples from the viper pit, and the necessary supplies of anti venom might add considerably to the cost. However, a suitable claw-ended retrieval pole might provide an adequate solution.

One hidden advantage of the pit technique – but for obvious reasons please keep this strictly *entre nous* – if you had a trainee Home Office inspector who was underperforming, but was difficult to remove from duty by the standard mechanisms, perhaps a little accident could be arranged: "Honest officer, he slipped. The side of the pit was wet".

We think this method has many positive aspects – ritual (a vital aspect of the end of life for humans), spectacle, and even the possibility of ticket and video sales. However, if you feel it is unworkable, the mouse and I do have other ideas we would welcome the chance to discuss with you. An electrified running wheel is one – clean, quiet, and carbon neutral if converted to solar or even to "running mouse" power. And I sense that we are only scratching the surface. The mouse has pointed out, rather perceptively I think, that humans have devised enormous numbers of creative ways of disposing of one another throughout history. So there must be many methods we could seek to adapt.

To close, if you are happy with our suggested method, please amend both my project and personal animal licence with immediate effect. It is our understanding that there is a longish lead time on orders for poisonous reptiles, and the mouse and I are keen to start testing and refining the method as soon as possible.'

And then, just as I was contemplating the best place to source half a dozen pit vipers, I woke up. And remembered I had to get to work.

A Home Office inspection is due, and we have to scrub the place from top to bottom, make sure all the forms and records are in order (all three filing cabinet drawers of them), and check that everyone's licences are complete and up to date. So back to reality.

But a man can always dream.

Keith Cormorant

The biochemical basis of the health effects of exercise

Essays in biochemistry No. 42

Edited by AJM Wagenmakers
2006. Portland Press, London.
214 pp, £21.95
ISBN 978 1-85578 159 7

If you are someone who likes schematic diagrams with lots of arrows, and various blobs or polygons representing genes, enzymes, substrates and so on, then you will love this book, which contains loads of them. To my mind they rather highlight the problems we face when trying to understand complex systems. On the one hand they are an undoubted help to learning. On the other, they spotlight how un-joined-up our thinking and analysis tends to be, so that once you've looked at more than a few you start to question whether you do in fact know anything worth knowing about the system after all. The blurb tells us that this volume 'gives clear mechanistic insights into the multitude of enzymes, signalling pathways and tissue and bodily functions that benefit from relatively modest increases in physical exercise, making exercise a unique and incredibly efficient therapeutic treatment.' Leaving aside the question of whether enzymes and signalling pathways can really 'benefit' from anything, this shows why you should never leave blurb writing to publishers. But is also reinforces the problem noted above. If all the book really says is that a bit of exercise is good for you, then you don't really need to read it. But, of course, there is more than this. There are 13 chapters (essays?) dealing with a variety of subjects related to the title, though principally focusing on the effects of exercise on gene expression, insulin action, fat metabolism and so-called metabolic syndrome. There are also contributions on muscle adaptation, mitochondrial biogenesis and muscle atrophy/hypertrophy. All of this is a well set out, if rather technical, read providing lots of information leavened by a healthy dose of schematics. The trouble is that there is so much data from diverse sources, that it becomes difficult or perhaps impossible to make much sense of it in relation to individual patients, except to say 'take more exercise'. While one can't disagree with the blurb writer's assertion that this volume will 'be a unique information source for medical doctors, health professionals, dieticians and public-health policymakers', I doubt many of them will read it, or would find it comprehensible if they did (the idea of public health policy being directly influenced by a volume such as this is terrifying). We should be honest about this sort of research. The main reason why we do it is not medical, it's cultural – it's because we like to try and figure out how things work. If something medically useful comes out of it, so much the better, but the likelihood is that it will in the end be subsumed by 'take more exercise'. The real audience for this book is not the blurb list, but researchers working in the field of muscle and exercise biochemistry and physiology. For them there is a lot of up-to-date material in this book, with a more than average amount of attempted synthesis. For them this volume represents good value for money and is worth reading.

John A Lee

The motoneurone and its muscle fibres

Monographs of The Physiological Society No. 50

By D Kernell
2006. Oxford University Press, Oxford. 341pp, £55.
ISBN 0-19-852655-5

In order to get things done, all our thoughts converge on motor neurones or, as they are for some reason called here, motoneurones (raising confusing crosstalk in my mind at least of mobile phones and motorway service stations). Be that as it may, it's an interesting fact that only one in every 200,000 neurones in the human central nervous system is a motor neurone, so it's not surprising that these rather special cells, mediators of the CNS 'final common pathway' should have excited a lot of interest. In fact, they are among the most intensively studied and best characterised of all mammalian neurones. They have large cell bodies which are relatively easy to get a microelectrode into, they can be clearly identified by stimulation of their peripheral axons, and they have clear functional tasks to perform on their also well characterised effector cells the muscles. A search for relevant papers from the last 55 years deluged the author with 19,700 references, which increased to 22,900 when he included the term 'motor unit'. Whew! Even though Daniel Kernell has been working in the field for 40 years, that still amounts to 11 papers every single week, including Christmas and school holidays. His aim in writing this monograph was to 'give a critical, balanced and reasonably complete survey of the most essential facts about motoneurone and muscle unit physiology, including both new and older observations, provided that they are all still valid' and to 'summarise the present state of affairs in a generally understandable manner'. Given the huge volume of work he has had to sift through (the book itself contains about 1,300 references), I think Kernell has done an excellent job. Introductory chapters deal with basic properties of neurones, neuromuscular transmission, muscles and motor units. Then follows more detail on motor neurone morphology, organisation, electrophysiology and synaptic control. Further chapters consider more integrative aspects of motor neurone physiology including motor neurone pools and the gradation of muscle force, fatigue and potentiation, denervation and its recovery, long term plasticity, and genetic control and lifespan development. The result is a close read which gives a pretty solid overview of the field. Although

people will be able to point to many extra details which could have been included in their own specialist fields, the overall result is impressive and will be of considerable interest and use to a wide range of readers, from those new to the field looking for a detailed introduction, to established researchers looking for new ideas or a wider context for their results.

John A Lee

Rhythms of the brain

By György Buzsák
Oxford University Press, Oxford. 448 pp, £42
ISBN 978 0 19 530106 9

György Buzsáki has written an excellent, scholarly book on brain oscillations, his speciality. The work is dense but very readable and is all the better for being by a single author rather than an edited collection of review articles. Appropriately, the book is divided into 13 cycles rather than chapters and each cycle ends with a brief and useful summary. He combines ideas from the neurosciences with those from chaos theory and non-linear dynamics, pointing out in the introduction (p. 13) that 'complexity can be formally defined as nonlinearity and from nonlinear equations, unexpected solutions emerge'. Put simply complex behaviour of a dynamic system such as the brain cannot be predicted from the behaviour of individual neurones or small neuronal ensembles.

György Buzsáki promotes the view that the inside-out approach to neuroscience enhances our understanding of relatively unperturbed brain states because ' self-generated behaviour and emergent large-scale oscillations tend to occur in the unperturbed brain'. In the introductory cycle he argues that during exploration of the brain, experimental perturbation of network interactions and emergent functions will yield hints of causality. He then successfully adopts this approach for much of the rest of the book. In cycles 2 and 3, György Buzsáki discusses form and function, indicating that preferentially connected areas of the cortex form the basis of higher order cortical systems, e.g. for movement and/or vision. He points out that the diversity of cortical functions can only be achieved by inhibition and by complex networks of interneurones offering the basis for temporal coordination, often accomplished by oscillations. In Cycle 4 (Windows on the Brain), he outlines the currently available monitoring techniques most frequently used to investigate the oscillatory behaviour of neuronal networks, including EEG, positron emission tomography, optical imaging, recordings from single neurones, and high density recordings with silicon probes. György Buzsáki's fundamental argument is that most of the brain's activity is generated from within and that external inputs cause only minor departures from its internal programme. Thus the brain 'does not simply process information but also generates information', observable in the EEG as a blend of rhythms unable to phase-lock with each other because their mean frequencies are not integers. These oscillations are metastable and result from the physical architecture of neuronal networks (cycle 5). In cycle 6 he discusses synchronization by oscillation based on self-organized interactions among neurones, which he argues may be the source of cognitive function. Cycle 7 discusses the self-organized oscillatory rhythms connected with rest and sleep – the default pattern of the brain in the absence of environmental inputs. In cycle 8 the perturbation of various default patterns by experience is explored and it is shown that sensory representations in the brain acquire real-world metrics early in development by first acquiring information about the three-dimensional nature of the skeletal muscle system. Cycle 9 considers the "Gamma Buzz" in the waking, activated cortex through which neuronal assemblies organize themselves into 'temporal packages' lasting 15-30 ms which may be involved in perceptual binding of object features. Buzsáki then goes on to show that perceptions and actions are brain-state dependent (cycle 10), which adds to his argument that a given environmental perturbation leads to modification of 'a perpetually evolving network pattern in the brain's landscape'. Cycle 11 talks of navigation in real and memory space and how the hippocampus is the search engine for the retrieval of archived information with theta oscillations related to episodic and semantic memory, path integration and 'map-based'/landmark navigation. Further transient oscillations are used to transfer this information to the neocortex, when cortical assemblies are transiently entrained to the theta rhythm (cycle 12). The final cycle investigates the relationship between structural connectivity and global function.

It is difficult to do justice to György Buzsáki's *tour de force* in a short review. I can only recommend that those with an interest in the neuroscience should read and learn from it.

Bill Winlow

Other books received

Regulatory mechanisms of striated muscle contraction. Advances in experimental medicine and biology No. 592. By S Ebashi and I Ohtsuki.

Oxford handbook of clinical examination and practical skills. Edited by James Thomas and Tanya Monaghan.

Oxford handbook of medical sciences. By Robert Wilkins, Simon Cross, Ian Megson and David Meredith.

Peer review and manuscript management in scientific journals. Guidelines for good practice. By Irene Hames.

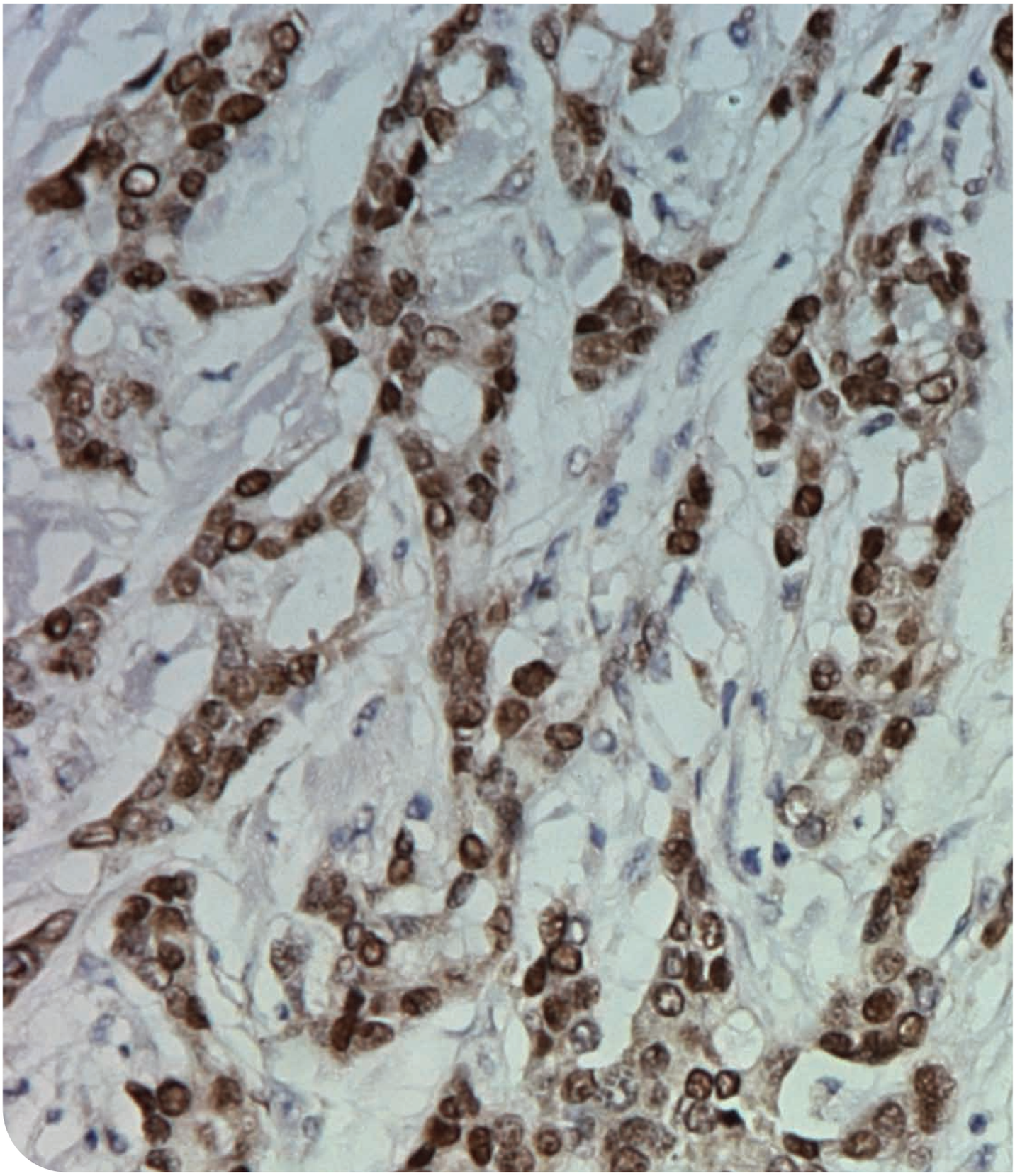
Insulin murders. By Vincent Marks and Caroline Richmond.

Neuro-ophthalmology. Edited by A Straube and U Büttner.

Reviews will be carried in future issues.

LifeSciences2007
8-12 July 2007, Glasgow, UK

Photos by Ivor Williams



Estrogen receptor in breast cancer. ER positive cells are stained brown and the section is counterstained with haematoxylin (blue). *Photo by Ms Korsa Khan, UCL*

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