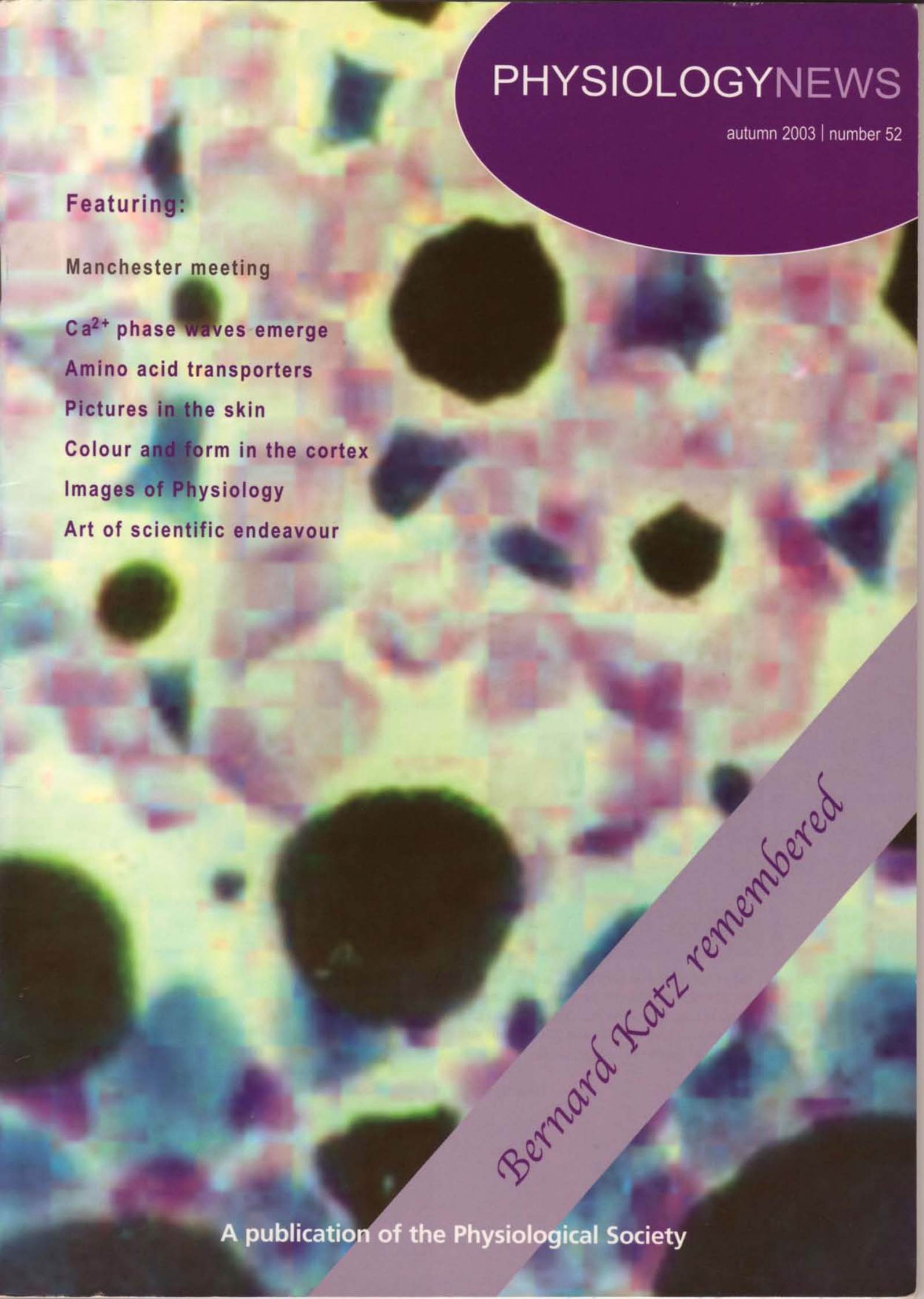

PHYSIOLOGYNEWS

autumn 2003 | number 52

Featuring:

Manchester meeting

Ca^{2+} phase waves emerge

Amino acid transporters

Pictures in the skin

Colour and form in the cortex

Images of Physiology

Art of scientific endeavour

Bernard Katz remembered

A publication of the Physiological Society

'My time is up and very glad I am, because I have been leading myself right up to a domain on which I should not dare to trespass, not even in an Inaugural Lecture. This domain contains the awkward problems of mind and matter about which so much has been talked and so little can be said, and having told you of my pedestrian disposition, I hope you will give me leave to stop at this point and not to hazard any further guesses.'

(closing words of Bernard Katz's Inaugural Lecture, 1952)

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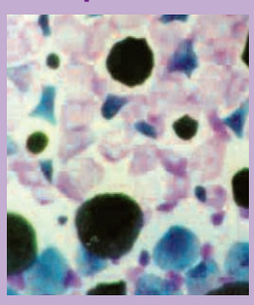

From an image supplied by Andrew Packard

PHYSIOLOGYNEWS

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Action Points

BSc Intercalated Bursaries
The main deadline for receipt of applications is 30 June (~10 awards), with a second deadline of 30 November (~3 awards) for institutions where projects are not decided until the course has begun.

Membership applications
The deadlines for receipt of Full Membership application forms during 2003 are the last day of September and December

Change of address
Members should inform the Administration Office of any changes of address, telephone, fax or email addresses.

Changes can be emailed to: jgould@physoc.org or updated online at www.physoc.org

Forthcoming scientific meetings

Manchester (9–12 September 2003)

Joint meeting with the British Pharmacological Society
Abstract submission period closed

Cambridge (17–19 December 2003)

Abstract submission period 15–24 September 2003

Glasgow (29–31 March 2004)

Abstract submissions
Authors should submit their abstracts online. Full instructions will be available on the Society's website (http://www.physoc.org/Meetings/future/html) from the opening day of the abstract submission period.

Physiology News

Letters and articles and all other contributions for inclusion in the Winter issue, No. 53, should reach the Publications Office by 2 September 2003. Late copy can be included if space permits.

Suggestions for articles

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

Physiology News Online

Physiology News is now available on our website: http://www.physoc.org.

Guidlines for contributors

These guidelines are intended to assist [illegible]g their contributions and [illegible]subsequent editing process. [illegible]rial Group of *Physiology News* [illegible]o 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 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 dénouement or conclusion.

Length of articles
This will be determined by the subject matter and agreed between the contributor and the commissioning editor. Articles will vary in length from 500 to 2,000 words.

Submission of articles
Authors should submit text in the form of a disk or emailed Word document accompanied by a printout wherever possible. Use of disks reduces the risk of introduction of errors during re-typing. It is helpful to give brief details of the computer, operating system and software package(s) used.

Submission deadlines
Please contact the Executive Editor in the Publications Office (see Contents page for details) for submission deadlines. Late submissions may be deferred to a subsequent issue.

Illustrations and authors' photographs
Authors are encouraged to submit diagrams, drawings, photographs or other artwork to illustrate their articles or, if they cannot provide these themselves, to suggest appropriate illustrations. A photograph of the author(s) should also accompany submissions.Photographs may be colour or black and white, prints or transparencies or TIFF 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 2003*, http://www.physoc.org).

In this issue

This issue of *Physiology News* is special in several ways.

One is that it contains an article looking forward to the upcoming joint meeting with the British Pharmacological Society (BPS). In the present scientific climate, closer links with our sister societies are critical to our success. The Physiological Society and the BPS share members, and many common interests, perhaps most critically in the future of *in vivo* research.

This issue also contains a hidden theme - the importance and richness of visual information and how it can be used in scientific investigation and communication. Thelma Lovick launches a new series on *Images of physiology*, with a range of examples you might not be expecting. Andrew Packard illustrates beautifully how looking carefully at cephalopods reveals incredible detail about their physiology, while Daniel Kiper reports on how the cortex processes colour and form. And you can also find out how to demonstrate important properties of the human visual system with an old shoebox (see *p*. 42).

Finally, the issue is truly special because it contains an appreciation of the life and work of Sir Bernard Katz, one of the giants of 20th century physiology, who passed away earlier this year. Quite apart from his towering scientific achievements, Bernard Katz lived a remarkable life, and David Colquhoun's obituary does it, and the man, full justice.

Magazine policy

It is one of the inevitable things about producing a magazine like *Physiology News* that it will, sooner or later, print something that is factually incorrect.

Sooner, if the editors are unlucky and the contributors are careless. Later, if the editors are lucky and the contributors are careful. But, eventually, something will get through. See, for instance, the letters column in the last issue.

This comes with the territory. A magazine, even one published by a learned scientific society, is not, can not and should not be a peer-review journal. The job of a magazine like *Physiology News* is to publish useful, informative, and hopefully also entertaining pieces that have something to do with physiology and physiologists and their concerns.

We could just fill the pages entirely with Society announcements, and reprint a few university press releases and articles borrowed from other publications. But why bother?

Instead, we are committed to bringing you something worth reading.

The people writing for *Physiology News* are asked to write what they think. What they think – not necessarily what the Society's Council thinks, or what the editors of the magazine think. Repeat: the contributors are not writing journal papers. But they are writing scientific content for a scientific readership.

Some are writing informative summaries of their own, or other people's, work, or discussing recent scientific advances, along the lines of News and Views articles in journals. Pure science, and a chance to put their work in a shop window in front of a highly informed scientific audience – you lot.

Others are writing more speculative pieces containing scientific hypotheses or arguments.

And still other contributors are writing, effectively, scientific journalism.

In these latter two cases - and especially the last one - does that mean the contributors don't check their facts? No.

Does it mean they can write any old rubbish? No.

Does it mean what they say is vetted to conform to an accepted view? No.

Does it mean they can write something completely one-sided? No – unless what they are writing is a letter, or is clearly a piece of advocacy or opinion.

In which case it will be identified as just that – as an opinion or personal view.

Getting back to the first point, what should happen when a magazine like *Physiology News* publishes something that is factually incorrect?

It should acknowledge the error, and publish, if appropriate, letters from the membership and anyone else pointing out the mistake.

And then it should move on.

Next, what about opinions expressed in the magazine?

Again, the answer is clear. If a writer expresses a view that other Society members disagree with, they have a way to respond – they should write in and disagree. The open debate that follows is a sign of a healthy magazine and of a healthy Society. An example of this can be seen in the article by Reade in *Physiology News* 49, and the response by Terry Bennett and Sheila Gardiner in the following issue.

That is how it is supposed to work.

Having said this, there are clearly limits. If someone has a personal axe to grind, they should not expect us to provide a forum for them. We will not publish anything deliberately inflammatory or derogatory. But beyond this, as far as possible, we are committed to not censoring anyone's views.

The other thing to say about *Physiology News* is that we are always looking for contributions.

Ideas for new features. Ideas for one-off articles. Ideas for themed issues. Cartoons. Jokes. Book reviews. Addresses of interesting websites. Anything.

Don't all write at once.

Or – do all write at once.

But either way, it's your magazine, so write!

Austin Elliott

Colin Blakemore

As this issue reaches the membership our President, Colin Blakemore, will be preparing to take up his new post as Chief Executive of the MRC on 1 October. All the members of the Society will want to extend congratulations to Colin on his appointment, and wish him the very best in this new role. Colin has always been a powerful advocate for biomedical research and for UK bioscientists. We cannot think of an individual better suited to head up this key agency.

Physiology and Pharmacology in Manchester

Top: Arthur Weston (Leech Professor of Pharmacology and co-organiser of the Circulation Symposium), above: Maynard Case (Dean of Biological Sciences) and below: Mark Dunne, the new head of 'PPT'

Following another reorganisation after the successful RAE 2001 result, there are now eight Divisions within the School of Biological Sciences. Many of the Societies' members belong to the School and are located in the Divisions of Physiology, Pharmacology and Toxicology (PPT), Neuroscience and Integrative Biology. Others work in the Stopford Building, but are members of the Faculty of Medicine and some of those currently at the University of Manchester Institute of Science and Technology (UMIST) will physically move to the Stopford site during 2004. It is difficult for insiders, let alone visitors, to keep track of all these changes but in the following paragraphs, I highlight some of the exciting on-going developments.

The merger with UMIST – Project Unity

The University of Manchester is merging with UMIST, a move which will significantly consolidate and strengthen biological sciences' education and research in Manchester. Formally the merger will be completed by September 2004 and, in these days of branding and imaging, the united institution may have a completely new name. Rumour has it that consultants are being paid large sums to formulate this and to design a new logo for the emerging institution. All that is certain is that September 2003 will see the very last meeting of our two Societies in the present Victoria University of Manchester.

The £50M ICMCB building in June, 2003. Occupation is scheduled for April, 2004

New buildings

When the Physiological Society last met here in March 1999, the so-called Incubator Building (for start-up companies) had just been completed and the Wellcome Clinical Research Centre was being planned. These are now established features of the landscape and were the forerunners of a massive bioscience building programme now underway around the Stopford Building. Thus, work will soon start on 'Incubator 2', the new Bioscience (ICMCB) Building (£50M) will be occupied during 2004, work on the MIB Building (£20M) on the UMIST site will soon start and the planning of the new Centre for Neuroscience (£20M) is well underway.

Teaching

Undergraduate teaching of Physiology and Pharmacology takes place under the auspices of the Medical Biosciences Board. If one includes the degree of BSc in Neuroscience in the calculation, approaching 200 undergraduates are currently being trained in Physiology and Pharmacology and many of them will graduate with one or both these names in their degree title. The figure is even larger if the BSc in Biomedical Sciences is taken into account.

The training of undergraduates in *laboratory* techniques has always been a Manchester strength and we have just spent nearly £500K on capital equipment for the multi-user teaching labs. Working closely with the Home Office and with the help of special funding from the Pharmacological Society and from Industry, our students continue to receive an unparalleled grounding in

in vivo techniques. With the Pharmaceutical Industry's increasing requirement for graduates with these skills recently highlighted (see Frantz (2003). *Nature Reviews, Drug Discovery* **2**, 801), our considerable investment in this aspect of their education is a major success.

There is continuing expansion of our four year courses in Physiology and in Pharmacology *with Industrial Experience*. Formerly known as Sandwich degrees, these provide an unrivalled 12 months' training in research and experimental design. From July 2003, 25 of the very best students in Physiology and Pharmacology (who have just completed their second year studies) will be studying outside Manchester in the UK, Germany, Switzerland and the USA. In our experience, it is from this group that the future leaders in Physiology and Pharmacology emerge.

A selection of personalities

Maynard Case is currently the Dean of Biological Sciences, a huge task made even more demanding by Project Unity. In spite of this, he and **Martin Steward** continue to explore the mechanisms of bicarbonate and water transport in the pancreatic duct and to use cultured epithelial cell lines as models for investigating the roles of acid-base transporters, aquaporin water channels and tight junction proteins.

An on-going strategy is to consolidate research efforts in the diverse field of receptors, ion channels and transporters. Work in **Peter Brown's** lab is focused on cation-chloride cotransporters while **Craig Smith's** group is clarifying the role of urea transporter proteins belonging to the UT-A sub-family. Five mouse UT-A isoforms have now been identified and structure-function studies are now under way.

Now well-established, **Daniela Riccardi** and **Donald Ward** employ a range of molecular and physiological techniques to investigate the role of the extracellular calcium-sensing receptor in cellular calcium homeostasis.

Caroline Dive (above, front row, far right) and her group (above) focus on the molecular mechanisms that couple the damage inflicted by anticancer drugs in tumour cells to the process of apoptosis. Craig Smith, Royal Society Fellow, and his group (below) are clarifying the role of urea transporter proteins belonging to the UT-A sub-family

Richard Prince who was recruited from the Mayo Clinic to work on the pharmacology of nicotinic cholinoceptors will shortly be joined by **Liz Fitzgerald** (from London) and **Kath Hinchliffe** (from Cambridge). These two new appointees will establish their own groups in the areas of calcium channels and lipid signalling, respectively.

Another recent appointment is that of **Gillian Edwards**. A research colleague of mine for many years, we continue to work on endothelium-derived hyperpolarizing factor and on the pharmacology of vascular potassium channels especially those with two-pore domain subunits.

Mark Dunne joined us on 1 March. He needs no introduction, being the Phys Soc's 2002/2003 GL Brown Lecturer and having only recently stepped down as the Society's Meetings Secretary. Mark has retained academic links with Sheffield and his research now embraces the area of developmental competence in the human fetal pancreas and the generation of insulin-secreting cultures from human embryonic stem cells. From 1 July, Mark will be the new Chairman of the Division of Physiology, Pharmacology and Toxicology.

Caroline Dive's group focuses on the molecular mechanisms that couple the damage inflicted by anticancer drugs in tumour cells to the process of apoptosis. One of her specific interests is whether c-Src, an oncogenic kinase that is routinely elevated in colon cancer can be modulated to promote drug-induced apoptosis. From September she will

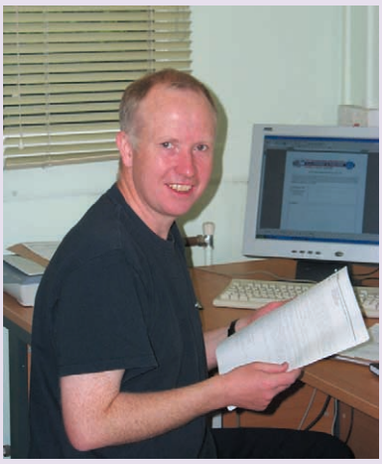
be based at the Paterson Institute where she will direct the cancer pharmacology labs.

Within the Division of Neuroscience, new appointee **Stuart Allan** is part of **Nancy Rothwell's** group investigating the mechanisms of neuronal death and the role of cytokines, particularly interleukin-1 and other inflammatory molecules.

Following his move to Manchester from Kiev, **Alex Verkhratsky's** lab is fully operational and dedicated to investigating the role of the endoplasmic reticulum in neuronal calcium signalling. These studies will lead to a better understanding of neurodegenerative disorders such as diabetic peripheral neuropathies and they complement those of **David Tomlinson** and **Paul Fernyhough**, both recent appointments from London. Their work on diabetic neuropathy should form the basis for the identification of novel drug targets and treatments for use in this widespread disease state.

Two further important developments are the recent appointments of **Risto Kauppinen** (from the University of Kuopio) and **Bagi Nadarajah** (from London). Risto is creating a new group of *in vivo* NMR brain imaging, the primary focus of which is the investigation of neurodegenerative disorders. Bagi is working on mechanisms underlying the development of the cerebral cortex with respect to neuronal migration and the early development of cortical neurones.

Shortly moving to the Stopford site will be **Graham Barnes** and his sensorimotor group from UMIST. Perhaps their most important achievement in recent years has been to demonstrate that the rapid predictive response observed in oculomotor control is accomplished through the combined action of short-term storage and timing estimation. They are currently investigating the limitations of sequence learning in hand and eye coordination and the role of cognitive factors in eye movement control.



Peter Brown (top) is Senior Lecturer in Physiology and organiser of the Transporter Symposium. Bagi Nadarajah (above) has recently begun work on mechanisms underlying the development of the cerebral cortex, with respect to neuronal migration and the early development of cortical neurones

Cardiovascular studies are well represented in Manchester and the work of **Richard Balment** and **Nick Ashton** (both in the Division of Integrative Biology) ranges from fish to mammals. Some of their current interests include altered Ca^{2+} transport in diabetes and the offspring of diabetic pregnancy, non-genomic actions of aldosterone and the cardiovascular and renal actions of urotensin II. Recent imports from Liverpool in the varying forms of **David Eisner**, **Stephen O'Neill** (convenor of the Phys Soc's Heart and Cardiac Muscle Special Interest Group), **Andy Trafford** and **Mary Díaz** are located in the School of Medicine**.** Their research interests range from the cellular mechanisms involved in the cardioprotective effects of polyunsaturated fatty acids to the phenomenon of *alternans*. Complimenting their cardiac studies are the vascular investigations of **Clare Austin** who is researching the link between calcium and vasomotion. Also involved in these vascular studies is **Mike Taggart** who is a member of the Maternal-Fetal Health Research Centre, along with **Colin Sibley** (convenor of the Phys Soc's Placental and Perinatal Special Interest Group)**, Sue Greenwood, Paul Speake** and **Mark Wareing.** Their work focuses on various aspects of pregnancy including placental function, myometrial contractility and control of vascular reactivity in mother and placenta.

Closing thoughts

In the above paragraphs, I have given a personal view of how Physiology and Pharmacology stand in Manchester. The old departments of Physiology and of Pharmacology may be long gone but the two subjects have never been in better shape. Applications for undergraduate places are buoyant, there are new faculty appointments, the research is '5-star' and we are building and innovating. There is a buzz and dynamism about the place which impresses all our visitors.

A warm welcome awaits you. Come and see.

Arthur Weston*

*Arthur Weston is Leech Professor of Pharmacology. He is a Trustee of the British Pharmacological Society and its Honorary Treasurer.

University of Newcastle-upon-Tyne, April 2003

A meeting of the Physiological Society, kindly sponsored in part by GlaxoSmithKline, took place in Newcastle-upon-Tyne during April. Those attending the dinner at the Baltic were lucky enough to have a preview of Antony Gormley's new work, Domain Field, as well as Allotment, Fruit, Body and Earth, which brings together for the first time three groups of his work made over the last 10 years. Those who missed it can visit:

http://www.balticmill.com/html/viean2.html

Ca^{2+} phase waves emerge

Biology continues to astonish even in well-studied areas. The discovery of long-range Ca2+ phase waves presents one such example. Dirk van Helden and Mohammad Imtiaz explain

Mohammad Imtiaz

Dirk van Helden

Lymphatic pacemaking

Evidence that Ca^{2+} phase waves can underlie both pacemaking and signal propagation has derived from studies on smooth muscle. My (i.e. DvH's) interest in pacemaking first arose during studies investigating the properties of spontaneous transient depolarizations in mesenteric veins. These events proved of particular interest as they were determined to be generated by spontaneous Ca^{2+} release events, each such event generating a spontaneous transient inward current (STIC) (van Helden, 1991) (Fig. 1). As such they presented a corollary to reports of spontaneous transient outward currents (STOCs) but now being excitatory. Adjacent to these vessels were lymphatic vessels that often exhibited spontaneous contractions. These vessels are divided into multiple chambers by unidirectional valves with each chamber acting as a 'primitive heart' to pump lymph. At this time (1986-89), there was little knowledge about the pacemaker mechanism in these 'hearts' and it was generally assumed that pacemaking arose through a cardiac-like pacemaker model involving cyclical activation of voltage-dependent channels in the cell plasmalemma. The temptation caused by observing the 'hearts' pumping away was too much and soon my microelectrodes strayed from the venous preparations to recording from the lymphatic smooth muscle.

Significantly these vessels, like the arteriolar preparations first prepared by David Hirst and Tim Neild and subsequently the small veins I had been working on, could be cut into electrically short segments. This meant that voltages generated by spontaneous or injected currents could be recorded with little decrement across the syncytium of smooth muscle cells. Indeed, in the mesenteric lymphatic preparation, some of the very short 'hearts' operated as independent electrically short preparations due to the smooth muscle being discontinuous in the region of the valves. Intracellular recordings made from electrically short lymphatic preparations led to the first major surprise, as action potentials were found to be generated by spontaneous transient depolarizations with properties analogous to those observed in the venous preparations (van Helden, 1993). Thus Ca^{2+} stores appear to control electrical pacemaking in these preparations.

The problem of store synchronicity

These findings, while most interesting, left one rather major perplexing problem. This was the problem of how stores could achieve sufficient synchronicity to drive large lymphatic 'hearts'. The much larger smooth muscle syncytium in such chambers exhibits very low input resistance and would require large currents to drive it, necessitating highly co-ordinated store release. How might stores achieve such synchronicity? The vein studies had shown that STICs show a broad range of amplitudes and could be very large, suggesting that there was substantial synchronisation of store release within and possibly across cells. Evidence for synchronisation of IP_3R-mediated Ca^{2+} release was also provided by the observation that a summation of these events could act as the lymphatic pacemaker potential, triggering the generation of lymphatic action potentials.

Synchronicity through diffusion-based Ca^{2+} waves - still insufficient

A possible solution to this mystery, was provided by the reports of Ca^{2+} waves where release from one store

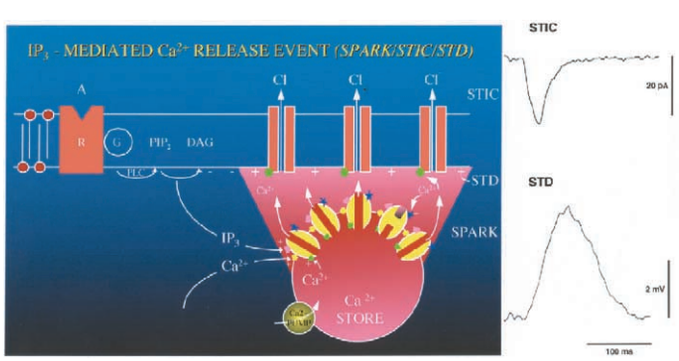


Figure 1. A Ca2+ release event in a lymphatic smooth muscle cell generates a spontaneous transient inward current (STIC) and resultant spontaneous transient depolarization (STD)

activates release of the adjacent stores. This occurs through calcium-induced calcium release (CICR) from either ryanodine receptors (RyRs) or inositol 1,4,5-trisphosphate receptors (IP_3Rs) present in the sarcoplasmic/endoplasmic reticulum of cells. Thus group activation of stores could occur by this mechanism which, in the case of lymphatics, would occur by sequential activation of IP_3Rs. However, there is a caveat even with this mechanism as Ca^{2+} waves have been reported to conduct relatively slowly (typically 0.002 - 0.1 mm/s) and would activate relatively few cells given the smooth muscle cell length is the order of 0.1 mm and Ca^{2+} release events and resultant STICs are brief (e.g. < 0.3 s). As such, even this mechanism is likely to be severely limited in its ability to induce sufficient current to drive guinea-pig lymphatic chambers to threshold, let alone those in the lymphatics of larger animals. Therefore, the question of how stores synchronise had not been resolved.

Slow waves also require massive store synchronicity

The pathway through this impasse came during a brief sabbatical visit to the laboratory of Hikaru Suzuki at Nagoya City University in the beginning of 1995. Here, I was introduced to recording slow waves in a visceral smooth muscle preparation and to the preparation of electrically tractable single bundles of this preparation, the latter provided by the much appreciated help of Takeo Itoh. While long studied, the origin of these waves was still unknown. A surprising similarity in the appearance of this activity to lymphatic pacemaker activity led to pharmacological experiments investigating a role for Ca^{2+} stores. Importantly, the results paralleled those of the lymphatics indicating that stores were driving pacemaking. This same approach was also applied to slow waves in the guinea-pig urethra resulting in the same outcome that stores were driving the slow waves (Hashitani *et al.* 1996). A key publication from Jan Huizinga's laboratory on the canine colon (Liu *et al.* 1995) arrived at the same conclusion, namely that Ca^{2+} stores were pacing slow waves.

Importantly, these findings were constrained by the same impasse. How could stores achieve sufficient synchronicity to pace the regenerative slow waves? Furthermore, in visceral smooth muscle there are additional complexities. First, the pacemaker cells are proposed to be a different type of cell termed Interstitial Cells of Cajal (ICCs), with one type present in specific networks in the myenteric plexus (ICC-MP) and another present intramuscularly (ICC-IM). Second, and most importantly, it was not known how the signal propagated across the vast number of cells to, in many cases, produce near synchronous contractions (e.g. circumferential contractions of the stomach including those of large animals are near synchronous providing optimum 'squeezing' of stomach contents). This does not occur by voltage-dependent channels commonly associated with action potentials, as slow waves occur and propagate in the presence of TTX or L-type Ca^{2+} channel blockade.

Synchronicity through coupled oscillators

A major advance to explaining the requirement for massive store synchronicity came when back in my own laboratory. There was an ongoing controversy of how slow waves propagate, with a cardiac type model (i.e. action potential-based propagation) contrasted against a long held alternative model, based on the concept of synchronisation of coupled oscillators. Coupled oscillator-based interactions were first described for an array of pendulums that, when linked (e.g. by springs) and randomly activated, entrain their activity over time. The result is a phase wave in which each oscillator has the same frequency of oscillation but with a spatial variation in phase that depends on the strength of the coupling between the oscillators. It is these principles that led to coupled oscillator-based models being applied to biological rhythms, as first applied to model heartbeats (van der Pol & van der Mark, 1926) and subsequently to interpret gastrointestinal slow waves While these models were mathematically based with no understanding of the underlying biological oscillators, they provided great interest and various research groups have continued to argue strongly for such mechanisms (e.g. see Daniel *et al*. 1994). This coupled oscillator model provided the next 'brick in the road' to understanding store synchronicity.

Diffusion-linked Ca^{2+} stores interact as weak coupled oscillators

Ca^{2+} stores are oscillators and are clearly coupled by at least one factor (i.e. the diffusion of Ca^{2+}) within and presumably across the cellular syncytium. We predicted coupling to occur through active stores undergoing oscillatory Ca^{2+} release advancing or retarding the cycle of adjacent stores by CICR until entrainment was achieved. It was time to undertake simulations of these interactions as made with Mike Sculley and subsequently with my graduate student Mohammad Imtiaz. To do this we used existing models used for modelling sequentially conducting Ca^{2+} waves involving a one-dimensional array of IP_3R-operated stores capable of oscillatory Ca^{2+} release as stimulated by IP_3 and/or Ca^{2+}. The primary difference was that we applied the stimulus globally over the tissue. The result was weak coupled oscillator-based synchronisation. An important paper appeared during this period, using the same type of simulation showing that Ca^{2+} waves in astrocytes could be explained as arising through Ca^{2+} stores interacting as coupled oscillators (Roth *et al.* 1995). In their case the coupled oscillator-based interactions, while weak, could explain the measured 'propagation' rates of the Ca^{2+} waves, which in their tissues exhibited 'apparent

conduction velocities' ('CVs') in the range 5-60 um/s dependent on the level of agonist stimulation and hence intracellular [IP_3]. Therefore, we were left with the conclusion that Ca^{2+} stores could interact as coupled oscillators, but such coupling was weak. This mechanism could not explain slow wave initiation due to the weak synchrony. Secondly, it could not explain slow wave propagation, with slow waves propagating with 'CVs' orders of magnitude greater.

Membrane voltage – the 'missing link'

The next step forward came through the outcomes of experiments being undertaken in the laboratory using finely dissected 'single bundle' strips of gastric pyloric smooth muscle (van Helden *et al.* 2000). Here, we presented evidence that slow waves were composed of a pacemaker and regenerative component, with both components generated by release from IP_3R-operated stores. Thus while the regenerative component of the slow wave outwardly resembles an action potential, it is not generated by voltage-dependent channels in the cell plasmalemma but by regenerative release from Ca^{2+} stores. Significantly, there is voltage-dependent feedback on IP_3R-mediated Ca^{2+} release, with depolarization enhancing and hyperpolarization decreasing release. This may result through voltage-dependent production of IP_3 but the same outcome would arise if the depolarization acted by an intermediate step, such as enhancing $[Ca^{2+}]_i$, with this intermediate then enhancing production of IP_3 (Fig. 2). Similar findings were also reported in strips of gastric antrum (Suzuki & Hirst, 1999).

The link between membrane potential and store Ca^{2+} release provided the key to solving the question of how stores could synchronise on a massive scale. Now stores are not simply linked by the diffusion of store activators alone but also by membrane voltage in its capacity to induce IP_3R-mediated Ca^{2+} release. Thus while the small effective diffusion range for Ca^{2+} of $< 10\ \mu m$ provides weak coupling between stores, coupling by membrane voltage is much more effective. This is so because membrane voltage and associated current flow has orders of magnitude more 'reach' than diffusion with electrical length constants typically in the range of 1–4 mm. The result is that active stores can now synchronise on a grand scale through long-range parallel interactions. It is this voltage link which underpins the emergence of long-range Ca^{2+} phase waves.

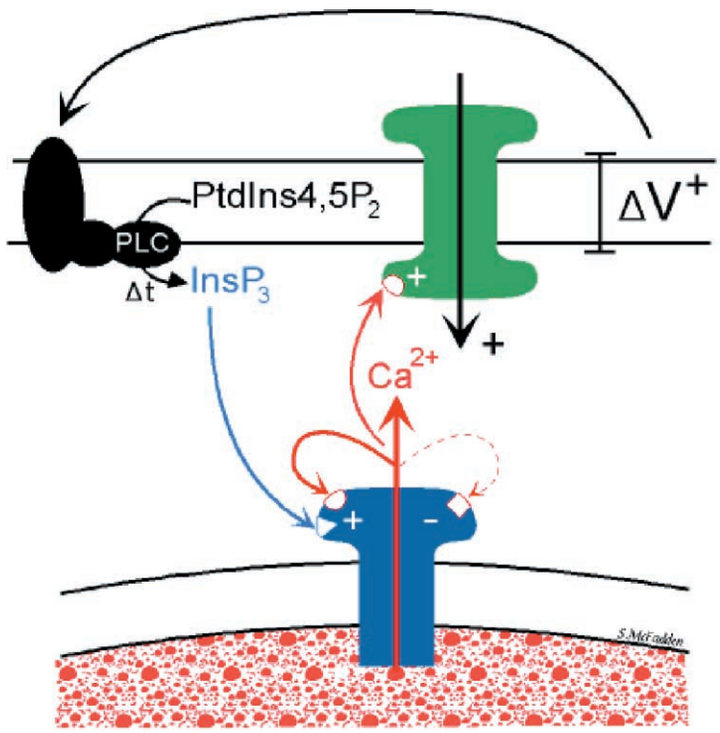


Figure 2. A schematic showing feedback linkages between IP_3R-mediated Ca^{2+} release and membrane depolarization. Store Ca^{2+} release depolarizes the membrane with this depolarization providing positive feedback to cause further IP_3R-mediated Ca^{2+} release from the SR (from van Helden *et al.* 2000)

Store synchronicity through long-range Ca^{2+} phase waves

Our recent paper and simulation (van Helden & Imtiaz, 2003) presents experimental and model-based evidence for the existence of these Ca^{2+} phase waves. The findings were again made using fine 'single bundle' strips of guinea-pig pyloric smooth muscle but now mostly using electrically long tissue strips of length up to 10 mm. Our view of how Ca^{2+} phase waves emerge in a previously quiescent tissue is as follows. Increasing stimulation of stores (e.g. agonist-induced increases in $[IP_3]_i$) across the cellular syncytium first activates the most sensitive sub-plasmalemmal IP3R-operated stores, the Ca^{2+} release events causing local inward current flow across the plasmalemma. Initially these act independently but as the level of stimulation increases local interactions increase to generate larger coordinated events underlying measurable spontaneous transient depolarizations. With further stimulation the number of these events increases across the cellular syncytium leading to more global synchronisation and resultant coordinated pacemaker Ca^{2+} release and associated pacemaker depolarization. As spatial synchronisation is imperfect, there is a phase delay between Ca^{2+} release across the array of stores and the pacemaker Ca^{2+} release takes the form of a Ca^{2+} phase wave. This is presented in the schematic of Fig. 3, which for simplicity uses a pendulum

analogy. Further stimulation and associated recruitment of stores, by the pacemaker Ca^{2+} release together with the associated depolarization, causes the sub-plasmalemmal [Ca^{2+}] and/or [IP_3] to reach threshold for regenerative activation of the large population of less sensitive stores. This results in regenerative Ca^{2+} release and associated slow wave potential. The Ca^{2+} phase waves are now much larger reflecting a pacemaker and a regenerative component with the average cycle time of the entrained stores determining the frequency and the phase delay the 'CV' of the resultant slow waves.

Part of the evidence for Ca^{2+} phase waves was based on a type of experiment made by A.L. Hodgkin in 1939. He found that alteration of the conduction pathway in a central region of a nerve axon modulated the action potential CV and in one case action potential conduction was interrupted dependent on the effectiveness of conduction in the central region. This latter observation is entirely consistent with the action potential conducting sequentially. In contrast, an analogous experiment performed on a strip exhibiting slow waves made by chemically interrupting the connectivity between cells near the middle of the strip did not stop transmission. Rather, the slow waves persisted at the two strip ends but now showed no phase correspondence with each other. This indicates that interactions are occurring by coupled oscillator-based mechanisms. A role of stores and the importance of electrical coupling between stores were indicated by central application of an inhibitor that blocks store release but does not interrupt cellular connectivity. This produced the same result but required a much wider central region of inhibition commensurate with the hypothesis that stores were primarily coupled by membrane voltage and not by diffusion of Ca^{2+}. In summary, the findings indicate that stores interact as coupled oscillators and that membrane potential is a key linking factor between the stores.

Simulations made by modelling the tissue as an array of IP_3R-operated stores with a Gaussian distribution of sensitivities mimic all the experimental findings. These simulations again confirm the fundamental importance of linking membrane depolarization to IP_3R-mediated store Ca^{2+} release. Significantly, the tissue can operate effectively independent of tissue size due to the distributed nature of the pacemaker, with each cell likely to drive its own regenerative response.

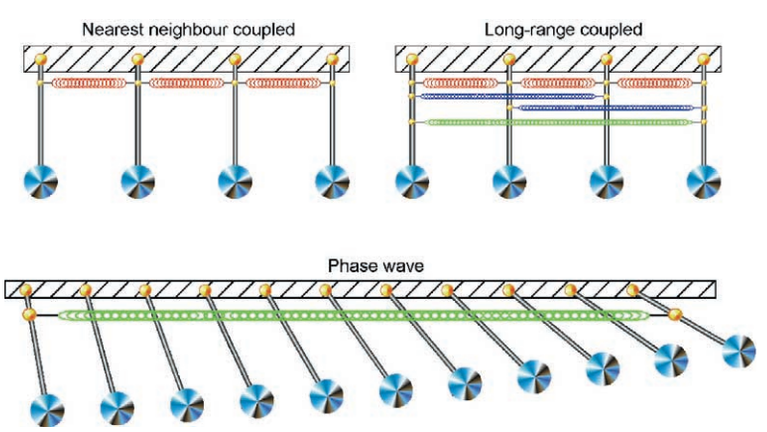


Figure 3. Coupled oscillators as exemplified by pendulums coupled by springs to their nearest neighbours. The effect of voltage-dependent IP_3 synthesis is illustrated by a system of pendulums coupled through multiple springs extending over the array of pendulums. These oscillators when randomly activated can entrain to produce a phase wave

The role of specific 'pacemaker cells' is also readily accounted for, these corresponding to cells that more readily undergo oscillatory Ca^{2+} release with their oscillatory cycle in turn entraining cells with less sensitive Ca^{2+} stores. Importantly, the proposed feedback between depolarization and production of IP_3 as used in the modelling studies indicates the co-existence of IP_3-phase waves. These are predicted to operate hand in hand with the Ca^{2+} phase waves.

Significantly, very high levels of agonist stimulation can cause desynchronisation and failure of slow waves. Our simulations suggest that this occurs because the frequency of store oscillations, which is known to increase with agonist concentration , becomes too high so that existing delays in the feedback between membrane voltage and store release become significant with resultant weakening in store coupling.

Lymphatic vasomotion

The same hypothesis can also be applied to lymphatics, as we together with Jun Zhao have recently communicated. The key to store synchronicity is again feedback between membrane depolarization. However, now the link is primarily due to depolarization induced opening of L-type Ca^{2+} channels and resultant calcium-induced calcium release from the stores. Ca^{2+} stores within the smooth muscle syncytium are now strongly coupled by membrane voltage and synchronise to produce pacemaker potentials that trigger action potentials and constrict the lymphatic 'hearts'.

Such constrictions are a type of vasomotion and in this regard it is interesting to note a recent hypothesis for vasomotion (Peng *et al.* 2001). Here initial uncoordinated Ca^{2+} release is considered to synchronise when 'sufficient number of cells become active at the same moment'. The resultant inward current now overcomes the current sink in the preparation and

depolarizes all cells to open L-Ca^{2+} channels, the resultant Ca^{2+} influx activating Ca^{2+} release across the cells. Significantly, Ca^{2+} phase waves provide a means by which biology ensures that sufficient number of cells do become active at the same moment. Consistent with this, there is direct proof in the literature that lymphatic vessels constrict through a coupled oscillator-based process. This derives from studies on bovine lymphatics (McHale & Meharg, 1992). Here central interference with pacemaking by either reduction in temperature or application of heptanol (10 mM), an agent likely to block intercellular connectivity caused the near synchronous contractions along the vessel to decouple.

Voltage-accelerated Ca^{2+} waves

A point made in our study (van Helden & Imtiaz, 2003) is that local stimulation of Ca^{2+} release could lead to production of accelerated sequentially conducting Ca^{2+} waves. This is considered to occur in the gastrointestinal smooth muscle through the voltage-feedback producing enhancement in IP_3R-mediated Ca^{2+} release, this process then continuing in sequence along the tissue. In the likely event that the feedback between membrane potential and IP_3R-mediated Ca^{2+} release is due to increased [IP_3], then there will be both a sequential voltage-accelerated IP_3 wave and resultant Ca^{2+} wave. However, while such rapidly conducting sequential waves are likely to be very important, the normal *modus operandi* of the rhythmically active tissues of our studies (i.e. pyloric and lymphatic smooth muscle tissues) is through stores interacting as coupled oscillators.

Future directions

Ca^{2+} and/or IP_3 phase waves may emerge to generate cellular rhythms when cells:

1. exhibit oscillatory IP_3R- or RyR-mediated store Ca^{2+} release;
2. depolarize in response to store Ca^{2+} release;
3. demonstrate increased store Ca^{2+} release upon membrane depolarization and
4. are interlinked through gap junctions or other pathways.

Physics tells us that arrays of oscillators that are strongly coupled entrain when sufficiently stimulated. Therefore Ca^{2+} stores in such cell systems should interact as strongly coupled oscillators, exhibiting emergent local near synchronous oscillations and long-range Ca^{2+} phase waves.

In such systems pacemaker frequency would be determined by the cycle time of the entrained stores and 'CV' by the synchronicity of the phase waves. As for the former, we note that Ca^{2+} phase wave-based pacemaking can theoretically exhibit an enormous range of frequencies (e.g. <0.1 to >10Hz), consistent with reported store cycle times. We also note that the 'CV' may also show a large range depending on factors such as the connectivity of cells and the strength of the positive feedback between membrane depolarization and store Ca^{2+} release.

Ca^{2+} phase wave-based pacemaking as presented here is sufficiently novel to allow some speculation. First, we predict it to underlie many cellular rhythms including specific brain rhythms, the brain being replete with both IP_3Rs and RyRs. Second, it seems possible that it will also have a role in heart pacemaking and conduction. We make this prediction based on growing evidence for a role of stores, as an important source of pacemaker current and through the strong linkage between membrane potential (i.e. voltage-dependent Ca^{2+} entry) and store Ca^{2+} release. Perhaps this store-based mechanism of pacemaking, as first observed in lymphatic 'hearts', may prove to be less 'primitive' than previously thought.

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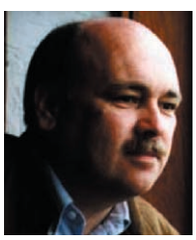
Role of cationic amino acid transporters in the regulation of nitric oxide synthesis in vascular cells

Anwar Baydoun and Giovanni Mann review the physiological and molecular characteristics of CAT transporters and discuss the role of L-arginine transport in regulating NO synthesis

Anwar Baydoun



Giovanni Mann

The discovery in 1987 that endothelium-derived relaxing factor is nitric oxide (NO) was followed a year later with reports that the cationic amino acid L–arginine is the physiological precursor for NO and in 1998 with the award of the Nobel Prize in Physiology and Medicine for the discovery of NO as a key signalling molecule. Several groups, including ours, have investigated the characteristics and regulation of cationic amino acid transporters (CAT-1, CAT-2A, CAT-2B, CAT-3) in vascular cells. In this article we review the physiological and molecular characteristics of CAT transporters mediating L–arginine influx and discuss the role of L-arginine transport in regulating NO synthesis. As there are several excellent reviews on the transduction pathways associated with NO biosynthesis and signaling, we aim to provide only a brief overview.

L–arginine-nitric oxide pathways

Nitric oxide is a free radical with a multitude of physiological and pathophysiological functions. Highly labile NO is synthesised from the cationic amino acid L–arginine following oxidation of the terminal guanidino-nitrogen by a family of enzymes referred to as NO synthases (NOS). Three distinct isoforms, endothelial (eNOS or NOS I), neuronal (nNOS or NOS II) and inducible (iNOS or NOS III), have been identified and are known to be derived from separate genes and regulated by diverse signalling pathways (reviewed by Alderton *et al.* 2001).

Both eNOS and nNOS are constitutively expressed, dependent upon Ca^{2+} and calmodulin for activation, and generate picomolar amounts of NO over short periods of time following agonist stimulation. Under normal physiological conditions, generation of NO via the constitutive endothelial L–arginine-NO pathway appears to be a key regulator of vascular tone, maintaining the vasculature in a basal state of vasodilatation. nNOS on the other hand mediates diverse neuronal functions accounting, for instance, for the nitridergic component of peripheral non-adrenergic, non-cholinergic neurotransmission.

In contrast to its constitutive isoforms, synthesis of NO via the inducible pathway involves induction of a Ca^{2+}/calmodulin-insensitive iNOS, previously identified in macrophages and now known to be induced in a wide variety of cell types including endothelial and smooth muscle cells. Expression of this enzyme is time-dependent, involves *de novo* protein synthesis and can be inhibited by protein synthesis inhibitors and glucocorticoids. Once induced the activity of the enzyme is sustained over prolonged periods and generates quantitatively more NO compared to its constitutive isoforms. Overproduction of NO by iNOS functions as an important mediator of inflammatory responses and has been implicated in the pathogenesis of various inflammatory and autoimmune disorders (reviewed by Hobbs *et al.* 1999).

Source of substrate for NO synthesis

The source of L–arginine for NO synthesis appears to depend on the physiological state and biosynthetic pathway being activated. L–arginine on it own does not significantly alter blood pressure *in vivo*, nor does L–arginine alter coronary perfusion pressure or the tension developed by isolated blood vessels *in vitro*. These findings suggest that basal NO synthesis is not limited by substrate availability. L–arginine is present in high concentrations in endothelial cells (~0.8 mM), and the K_m of eNOS for L–arginine is <0.01 mM, with maximal stimulation occurring in the presence of 0.03-0.1 mM L–arginine. Thus availability of L–arginine may not be rate limiting for the relatively small quantities of NO released under basal conditions. The same appears to be true for transient stimulation of NO production by various agonists, including bradykinin and acetylcholine. However, when a stimulus is applied repeatedly over prolonged periods, endogenous substrate becomes rate limiting. Under these conditions availability and transport of exogenous L–arginine restores responses previously rendered tolerant by repeated or prolonged agonist administration. In this context, studies in cultured endothelial cells, perfused tissues, whole animals and man have shown that exogenous L–arginine can reverse inhibition of

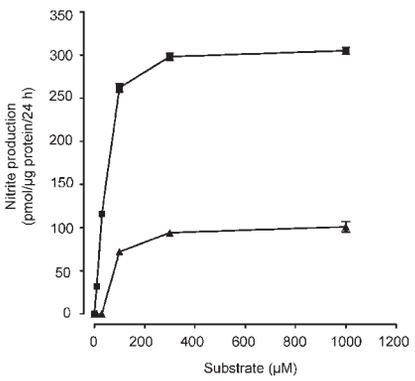


Figure 1. Dependency of LPS/interferon-γ stimulated nitrite release from rat aortic smooth muscle cells on extracellular L-arginine or L-citrulline. Rat aortic smooth muscle cells were activated for 24h with LPS (100 µg ml^{-1}) and IFN-γ (50 U ml^{-1}) in L-arginine-depleted medium supplemented with increasing concentrations of either L-arginine (■) or L-citrulline (▲), with nitrite accumulation used as an index of NO production.

eNOS by inhibitor analogues of L–arginine itself, and enhance or sustain agonist-induced release of NO from the endothelium. Interestingly, the endothelium-dependent component of cyclic AMP-mediated relaxation in rat pulmonary arteries is critically dependent on availability of extracellular L–arginine (see Hucks *et al.* 2000).

The dependence of NO production on exogenous L–arginine is perhaps more apparent with iNOS, the high output system that generates nanomolar quantities of NO over prolonged periods. Release of NO by this enzyme is not only dependent on the presence of extracellular L–arginine, but also directly related to the rate of L–arginine transport.

These findings suggest that availability and transport of L–arginine can limit NO production under both physiological and pathophysiological conditions. There are, however, counter arguments, since vascular cells can metabolise L–citrulline via a truncated urea cycle to generate adequate amounts of L–arginine for sustained NO synthesis. Consistent with this hypothesis is that conversion of L–citrulline to L–arginine is enhanced in endothelial cells stimulated to release NO, as well as in macrophages and smooth muscle cells generating NO following activation with pro-inflammatory mediators. However, despite these increases in the generation of L–arginine from L–citrulline, our studies in intact cells have shown that in L–arginine deprived cells L–citrulline cannot sustain maximal rates of NO synthesis (Fig. 1). Moreover, as transport of L-citrulline into vascular cells is slow and 3-fold lower than rates measured for L–arginine, it seems unlikely that L–citrulline transport can sustain maximal rates of NO synthesis *in vivo* (Wileman *et al.* 2003)

Modulation of L–arginine transport by nitric oxide

The critical role of exogenous L–arginine in regulating NO production begs the question of whether NO can modulate transport of L–arginine. Influx of L–arginine is increased transiently in endothelial cells stimulated with NO releasing agonists such as bradykinin, ATP or adenosine and elevated in cells expressing iNOS. Recent studies have shown that the NO donors (SNAP, dipropylenetriamine NONOate) acutely stimulate L–ARGININE influx, whereas longer exposure (1-4 h) to these NO donors inhibits transport. The inhibitory effects of prolonged NO exposure on L–arginine transport were attributed to the oxidation of sulfhydryl moieties within the transporter protein. At present there is limited evidence to suggest that L–arginine transport and NO synthesis are directly coupled. Instead, these two processes may be regulated independently since (i) increases in L–arginine transport occur despite inhibition of iNOS expression by dexamethasone, (ii) inhibition of iNOS with arginine analogues such as L-NAME does not alter cytokine-stimulated L–arginine transport in cultured cells and (iii) transfection of iNOS cDNA in cells which do not express iNOS either constitutively or in response to pro-inflammatory mediators (e.g. HEK293 cells) fails to cause significant changes in L–arginine transport despite a significant increase in NO production (unpublished observations). These findings argue against regulation of L–arginine transporter function by the activity of iNOS.

Based on the evidence available, it seems that enhanced L–arginine transport in iNOS expressing cells requires *de novo* protein synthesis. This may result from the activation by external stimuli of key kinase signalling cascades of which the p38 mitogen-activated kinase pathway may be critical (Baydoun *et al.* 1999). In contrast, transient increases in L–arginine transport observed in agonist-stimulated endothelial cells may be secondary to a membrane hyperpolarization induced by vasoactive agonists (Fig. 2). Nevertheless, we would still like to postulate that increased cationic amino acid transporter activity provides a mechanism for sustaining

Table. Characteristics of cationic amino acid transporters

	CAT-1	CAT-2A	CAT-2B	CAT-3
K_m (mM)	0.07-0.25	2.1-5.2	0.04-0.38	0.04-0.12
Na^+-independent	yes	yes	yes	yes
Amino acids	629	657	658	619
MW (kDa)	67	72	72	67
N-glycosylation	yes	yes	yes	yes
Expression	constitutive	constitutive	inducible	constitutive
Key cell type	ubiquitous except liver	liver, muscle,skin	T-cells, macrophages	brain

L–arginine supply during prolonged NO production.

Transport systems mediating influx of L–arginine

L–arginine is predominantly transported across cell membranes via specific sodium-independent transporter(s) selective for cationic amino acids. This pathway was originally termed system y^+. Although other systems, including b^+, $b^{o,+}$, $B^{o,+}$ and y^+L, have been identified as transporters for cationic amino acids, these carriers also accept a wider range of substrates, including neutral amino acids (Devés & Boyd, 1998). Thus, the only selective cationic transporter expressed in vascular cells still remains system y^+.

System y^+ was initially thought of in terms of a 'one-protein-one transport activity' paradigm. However, the evolution of recombinant DNA technology and the development of new kinetic experimental approaches have unveiled a more complex picture. It is now evident that transport of L–arginine, and indeed other cationic amino acids, involves several distinct proteins which are distinguishable by their structure, distribution and affinity for cationic amino acids.

At least five different CAT proteins designated CAT-1, CAT-2A, CAT-2B, CAT-3 and CAT-4 have been identified in different mammalian tissues. Some of the key characteristics of these proteins are discussed below and summarised in the Table. CAT-4 appears to lack cationic amino acid transport activity, and CAT-3 is expressed predominantly in brain and thymus tissue and also interacts with neutral amino acids.

Molecular identification, structure and function of CATs

Of the five proteins, CAT-1, a high-affinity electrogenic transporter, was the first to be characterised at a molecular level. This protein was cloned serendipitously by a group searching for the ecotropic murine leukemia virus receptor (ecoR), and shown to mediate cationic amino acid transport when expressed in *Xenopus* oocytes. The deduced amino acid sequence of the cloned cDNA revealed a 622 amino acid glycoprotein of about 67 kDa with 12 to 14 transmembrane spanning domains.

A truncated *CAT-2* gene was cloned shortly after *CAT-1* and initially named Tea (T-cell early activation receptor) because of its induction early in the response of normal T cells to mitogens. The full length cDNA which encodes a 658 amino acid protein (CAT-2B) was subsequently isolated and shown to have a 61 % homology with CAT-1 (see Table) and 98 % homology with CAT-2A. It is now known that CAT-2A and CAT-2B are the products of differentially spliced mRNAs. The deduced sequence of these two proteins differ by only 20 amino acids within a stretch of 41 amino acids in an alternatively spliced region in the predicted fourth extracellular loop.

Unlike CAT-1 and CAT-2A, CAT-2B is an inducible protein (at least in macrophages) with a high affinity for L–arginine (K_m: 0.04 - 0.38 mM) comparable to that of CAT-1, despite its high sequence identity with CAT-2A. This strongly indicates that the divergent domain in the predicted fourth loop of CAT-2 may be critical for substrate recognition and/or translocation. Indeed, substitution of this domain in CAT-2B with that of CAT-2A resulted in a chimeric protein that had a low affinity for L–arginine, while substituting this domain in CAT-2A with that of CAT-1 or CAT-2B resulted in a transporter with high affinity for L–arginine comparable to that of CAT-1 and CAT-2B. These variations in transport properties have recently been attributed to differences in two amino acid residues within the stretch of 42 amino acids in the alternatively spliced region of the human CAT isoforms (Habermeier *et al.* 2003).

At present we cannot distinguish between CAT-1 and CAT-2B in terms of their relative contribution to total L–arginine uptake under

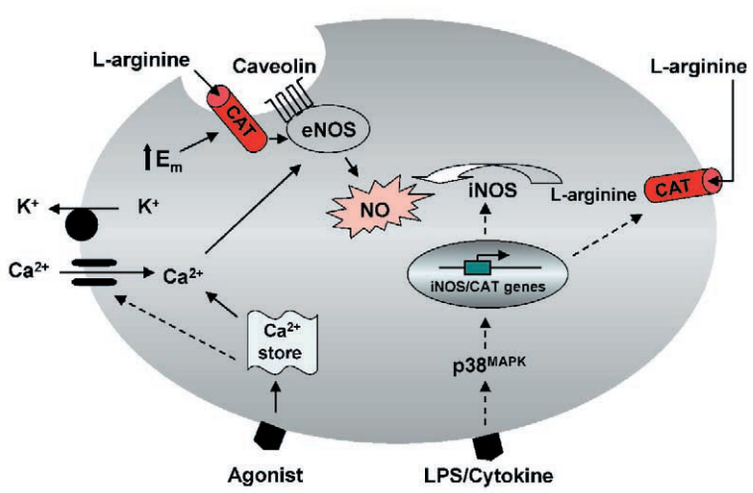


Figure 2. Relationship between L-arginine transport and NO synthesis in vascular cells. Stimulation of endothelial cells with agonist elevates intracellular Ca^{2+} and activates both eNOS and Ca^{2+}-activated K^+ channels, with the latter resulting in a membrane hyperpolarization and increased transport of L-arginine via CAT(s). Treatment of cells with LPS/cytokines activates specific signalling mechanisms, leading to the induction of iNOS and synthesis of new CAT proteins involved in the supply of extracellular L-arginine to iNOS for NO production

normal physiological conditions, nor can we specify which CAT directly supplies L–arginine to NOS in cell system. This latter point is important since there are reports that CAT-1, by virtue of its co-localisation with eNOS in membrane caveolae supplies substrate to this enzyme (Fig. 2), whereas CAT-2B, which is induced in parallel with iNOS, critically regulates supply of L–arginine to this enzyme. Moreover, the finding that iNOS mediated NO production is significantly reduced in peritoneal macrophages from CAT-2B$^{-/-}$ mice (Nicholson *et al*. 2001), strongly suggests a functional association between CAT-2B and iNOS, and a critical dependency of NO production on L–ARGININE delivery at least in peritoneal macrophages.

The notion that different NOS isoforms may be directly linked to distinct CAT(s) for substrate supply should however be viewed with caution, since this may be cell type dependent. Using isoform-specific probes in RNase protection analyses, we have identified transcripts for CAT-1, CAT-2A and CAT-2B in rat primary aortic smooth muscle cell cultures. Moreover, significant elevations in mRNA for all three CAT isoforms were detected following activation of cells with LPS and interferon-γ (Baydoun *et al.* 1999). Enhanced transcript levels for CAT-1, -2A and -2B have also been observed in cardiac myocytes following treatment with IL-1β and IFN-γ (Simmons *et al.* 1996). These findings have now lead to the realisation that transport of L–arginine may be more complex than the initial "one-protein-one transport activity" paradigm, and raise the question of the specific contribution of each CAT to total L–arginine transport in different cell systems. Specific knockouts and/or antisense strategies are clearly required to identify the key CAT(s) associated with the regulation of NO biosynthesis.

Conclusions

The identification of distinct transport proteins that mediate influx of L–arginine provides a basis for assessing the role of these transporters in regulating NO production, though questions remain concerning the signal transduction pathways involved in the co-activation of L–arginine transport and NO synthesis. Future understanding of the compartmentalisation of different CATs may permit the design specific probes that could be used to selectively manipulate expression and/or function of different CATs. This would undoubtedly allow for the physiological role of these proteins and their involvement in various diseases to be established. Indeed there are indications that altered L–arginine transport may contribute to the pathophysiology of cardiovascular disorders. Acute administration of L–arginine restores endothelium-dependent vasodilatation in hypercholesterolemic patients, and both acute and chronic administration of L–arginine also normalises impaired endothelium-dependent relaxation in vessels isolated from cholesterol-fed rabbits. Recent evidence indicates that pregnancy-associated diseases, such as gestational diabetes, intrauterine growth retardation and pre-eclampsia, can induce phenotypic changes in the fetal vasculature which result in alterations in the L–arginine-NO signalling pathway (see review by Mann *et al.* 2003). Advances in the molecular biology of cationic amino acid transporters and intracellular signalling pathways provide a basis for further investigating the regulation of L–arginine transport in NO generating cells in health and disease.

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Not for giant axons only

Pictures in the skin. Insights into fundamental functions from familiarity with the whole

by Andrew Packard

Andrew Packard

Figure 1a (above) and **1b** (below) from Cowdry (1911)

Figure 2. Squid swimming in holding tank two days after cutting the pallial nerve (on near side)

It is not just for ethical and legal reasons that most laboratories have abandoned the whole animal approach to physiology. So perhaps I have been unusually lucky that my squids have still to be closed off on the far side of the animal house door in the name of tidiness and division of labour. That I am able to practise the art that served our predecessors for hundreds of years: feeding, caring, and generally getting to know each experimental individual: part of a procedure I have called ontophysiology. For with cephalopods, where colour is concerned (Packard, 1995 for summary), one can follow activity simultaneously at the behavioural and at intermediate levels down to the cellular. It is simply a matter of appropriate magnification – and of attitude.

The field is wide open and the intellectual rewards of letting the animal tell its own story are great.

Access to brain functions through the systematics of colour: the whole informs the parts

Edmund V.Cowdry (1888-1975), is better known for his contributions to medicine than for constructing an 'octopus car' when an anatomy student at the University of Toronto. His faithful water-colours of octopuses placed in this device in front of the marine biological station of Bermuda (Figure 1a,b) are amongst the first attempts to classify the patterns of cephalopod molluscs (Cowdry 1911). Commuting between Plymouth, Oxford, London and Naples in search of cuttlefish and octopuses, J.Z.Young, William Holmes and Brian Boycott added to the catalogue over the years. (Young's drawing of the male of a local species displaying to a female, spotted while snorkelling between sessions of external examining in Singapore, is one of the few records of octopus courtship). So when Geoff Sanders,Young's psychology assistant in Naples, walked into my office with an armful of notes on the various postures and patterns observed during training experiments, he was unknowingly continuing the tradition of noting down – and *sketching* – any new natural behaviours seen during the course of experiments on quite different things.

Our job was to fill the gaps in the ethological description and classification, and to *parse* the patterns. Boycott had obtained

'It is hard to believe that the sudden bleaching which occurs when the animal is poked with a stick is purely passive, and results, simply, from the elasticity of the walls of the chromatophores. Similarly, [with] the abrupt appearance of the long white stripes [Fig.1b right]… the possibility remains that the bleaching may be fundamentally passive and result from the inhibition of the impulses passing from the central nervous system to the chromatophores; but if this is the case we should have to assume that in the normal light gray coloration of the resting animal [Fig.1a upper left] the chromatophores are continually receiving impulses from the brain and that consequently the radial muscles are always in action, for we meet with a still lighter coloration as illustrated in [Fig.1a lower right]… The conclusion is therefore justified that, although the anatomical findings seem to show conclusively that the diminution in size of the chromatophores is purely passive and results from the elasticity of their walls, still close observation indicates that this may not be the case.'

Cowdry (1911)

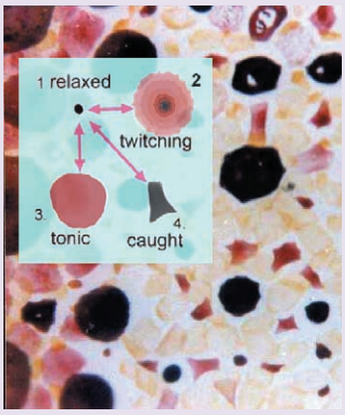

Figure 3. Different muscle contractile states signalled by the shapes of spots (*Loligo vulgaris* dorsal mantle post mortem) (approx. x8 natural size)

centrally induced expressions of colour by electrical stimulation of motor centres in the brain, and before him Enrico Sereni (Young's mentor when he was Oxford scholar at Naples) had tried pharmacological stimulation: a route later adopted by J.B.Messenger and colleagues. It was a short step to discover that the irreducible (parsed) components of the patterns corresponded to hard-wired units in brain and skin which could be topically stimulated with an exploring electrode.

At which point I naturally turned to the isolated skin, only to find – lesson number one – that the isolated

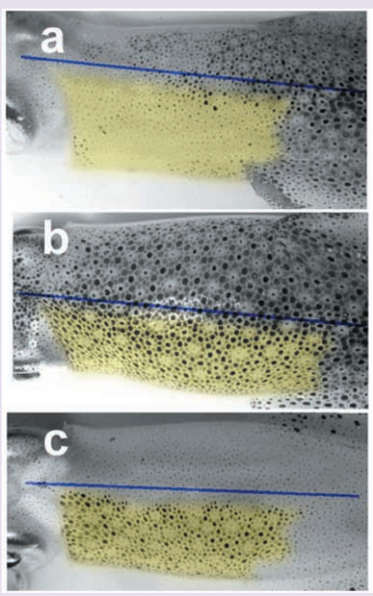

Figure 4a-c. Unstable configurations of myogenic activity on the flank of a squid (highlighted) three days after nerve section. Colouration of the rest of the body is driven by the brain

preparation behaves very differently from, and much less reliably than, the animal in its entirety.

Unilateral denervation...

Although something of the wonder is now lost to us, the Belgian physiologist Léon Fredericq (1851–1935) – who also was a talented water-colourist (!) – discovered that when he reached through the breathing aperture of an octopus to cut the pallial nerve on one side, half of the mantle immediately went pale. The same approach was used by Sanders and Young (1978) to very good effect in a rarely quoted study of pattern *regeneration*.

The paling of the skin following the initial cut does not last, however. At two days, as the mixed pallial nerve degenerates and denervation supersensitivity develops in the chromatophore muscles, the operated side gradually becomes dark brown (compare Fig. 2).

... and the myogenic signs that result

Chromatophores (spots) are much larger in squids than in octopuses. The skin receives oxygen directly through a surface of exceptionally good optical quality, so that individual and collective signals generated by muscular tension on the spots can be recorded at relatively high resolution (Fig. 3) and for many hours (even days) following brain death. The tonic darkening of denervation supersensitivity (DDSS) is best seen when the rest of the animal is pale (Fig. 2 & 4c). Each spot in these configurations has a round profile, roundness resulting from equal and synchronous contraction of most (or all) of the 20 or so radial muscle fibres supplying any given chromatophore. These muscle fibres are coupled and their syntony and synchrony are myogenic.

Nevertheless, the configurations are remarkably similar to patterns also seen on the intact side (Fig. 4b), as if the nerve had never been cut – or as if those normal patterns were also myogenic!

Subsequently (four to eight days depending on temperature) DDSS gives way to coherent but irregular waves of twitch contractions propagating at ~1 cm/s throughout the denervated territory - sign that nerve degeneration is complete. Like the tonic configurations, which can be regarded as slow or standing waves of contractile state, these fast waves exhibit chaotic dynamics.[1]

Development the key to understanding coupled ensembles

Fortunately, there are some simple rules for reducing the complexity of the picture at this stage, when everything seems to be communicating with everything else. In cephalopods, as if their other gifts to the experimenter were not enough, the ontogenetic history of each chromatophore organ is encoded in its position, in its size and in its colour (largest-darkest oldest, smallest-lightest youngest) (Fig.5).

With this knowledge, it takes only a few seconds of the hundreds of hours of videorecordings of myogenic automaticity to realize that waves tend to run selectively through yellow, orange, red, and brown spots (of several sizes) lying in closely superimposed networks. *Within* any one network, connectivity (measured as probability of transmission of contractile state) is normally 100%. Between colour classes it is differential.[2]

I have given the name *homeotaxy* to the observed conformity of behaviour among elements of a given developmental class when freed from nervous control. It persists for as long as the skin remains alive. Is homeotaxy (Greek: same arrangement, or peer conformity to give it an English name) a characteristic of waves propagating through other coupled ensembles?

Complementary roles of spots in pattern generation...

Recently, squids have helped resolve a problem that had plagued me for decades. One class of pattern – in Nature as in Art – consists of both figure and ground. The tattered bar that appears across the front of the mantle when a squid is hiding near the bottom of the tank (Fig. 6) is one such feature (F). It behaves more or less like classical motor units being generated by twitches and tetani that expand certain dark spots. Increases in frequency of firing increase both the sizes of individual spots and the numbers of spots responding: a process of spatial recruitment. Many of these spots have *polygonal* profiles in close up view (Fig. 6): the shape telling which of the 20-25 muscle fibres surrounding each spot are developing tension. However, the many *featureless* uniform and graded colours in the repertoire of squids, which also furnish the ground (G) to these bars, are not organised in clear-cut motor units. They are built up of *round* spots – like the myogenically expanded spots encountered in denervated skin.

Opponent processing for the *perception* of contrast – necessary also for the discrimination of figure and ground – occurs early on in the vertebrate visual pathway, classically through lateral inhibition. Contrast is *generated* in the skin of octopuses, by what appears to be lateral inhibition, in situations of behavioural conflict and as a major component of camouflage patterns (Packard, 1995). There has long been an argument whether chromatophore muscle fibres receive inhibitory innervation, though none has ever been found. After carefully comparing the colour of a pale octopus on a sandy ground and when 'frightened' (a pattern now known as dymantic, or deimatic) the young Cowdry concluded that there was some form of inhibition: though not necessarily nervous (see Box p.16).

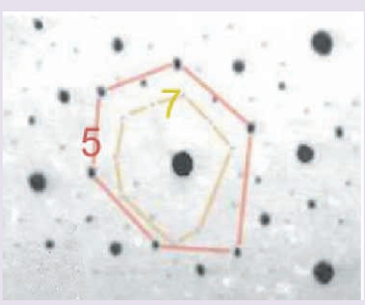

Figure 5. Fully retracted spots in a living *Loligo*. Two colour networks indicated (5,7)

How active, rather than passive, relaxation of chromatophores is achieved is still not clear. But the whiteness of contrast – and of the 'frightened' octopus – can be simulated by subcutaneously injected serotonin and by the nitric oxide donor DEANO.[3] The reaction propagates as a slow wave of relaxation and is stronger in denervated than in innervated skin.

... mediated by reciprocal inhibition between muscle fibres?

Generation of features (F) against a clear ground (G) through opponent processing need not in principle involve nerves. One piece of evidence for its occurring as reciprocal inhibition between different muscle fibres is shown in Figure 7 presented at last year's LiverpooI meeting (Packard, 2002). I have since found that the phenomenon, regularly seen post mortem when the nerve has died or become anoxic, also occurs in the operated half of a long-term unilaterally denervated mantle, i.e. in the total absence of innervation.

If reciprocity is occurring between two muscle fibre types – either directly or indirectly through an interstitial cell layer – this would be a new finding for muscle generally. It would make sense. Most visceral and other kinds of muscle in the animal kingdom is in blocks that require relaxation of muscle in some directions while those in the orthogonal are contracting. Fundamental properties such as this have not evolved just for generating pretty pictures in the skin.

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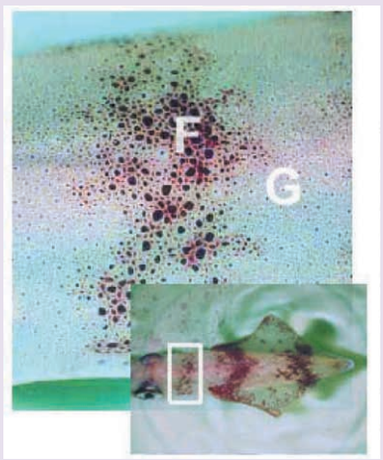

Figure 6. Tranverse bar feature (F) of the cryptic pose adopted by Loligo.

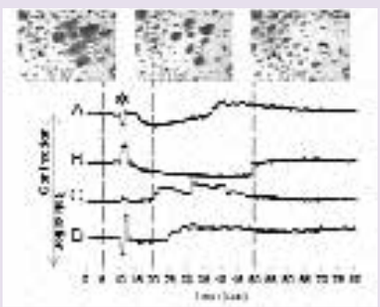

Figure 7. Relaxation of 'caught' profiles (A,B) in response to a brief seawater pulse (*) induces phasic/tonic contractions in neighbouring spots (C,D). Video-frame traces from Packard, 2002). (Loligo vulgaris six hours post mortem)

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Notes

[1] An exhaustive description of these waves requires video clips and has never been published. Some may be consulted on http://www.gfai.de/www_open/perspg/g_heinz/biomodel/squids/squids.htm others on CD from the author.

[2] Fast waves can be reversibly interrupted by topically applied heptanol (which is both anaesthetic and gap junction blocker). RF frequencies from a mobile 'phone interfere with their generation. For an eye-opening introduction to mechanism(s) that might be involved in these (usually hidden) kinds of horizontal conduction, I recommend the review of Ho and Knight (Ho M-W & Knight DP (1998). The acupuncture system and the liquid crystalline collagen fibres of the connective tissues Am J Chin Med 26(3-4), 251- 263.

[3] With thanks to Anna Palumbo.

Colour and form in the cortex

Descriptions of primate visual cortex suggest that object's colour and orientation of its contours are analyzed by independent, anatomically segregated neural populations. Recent results, however, show that cortical neurons can simultaneously code for both attributes. Cortical neurons, as Daniel Kiper explains, are thus ideally suited to analyze real scenes, where luminance- and coloured-defined contours are highly correlated

Daniel Kiper

When a human observer looks at an object, perception of the object is elicited by the activity of numerous neuronal populations. Most visual neuroscientists today would agree on the neuronal events occurring in the first stages of the visual system. The light reflected from the object's surface reaches the observer's eyes, where it is transformed into electrical signals by the photoreceptors of the retina. In daylight, three classes of cone photoreceptors respond differentially to the wavelength composition of the incoming light, thereby providing the physiological basis for our trichromatic color vision system. After processing by the retinal network, the signals representing the object are sent through the optic nerves towards the lateral geniculate nucleus (LGN) of the thalamus. The retinal ganglion cells and LGN neurons represent the object's physical properties in roughly the same way: a population of cells sensitive to local luminance variations signals the object's contours, while the object's colour is represented in two distinct channels: one sensitive to red-green modulations, the other to blue-yellow (Derrington er al. 1984). Thus, in the retina and LGN, signals coding for the object's physical attributes are treated by separate, distinct neuronal populations. Upon reaching the primary visual cortex (V1, striate cortex), the fate of the signals is more mysterious. Neuroscientists disagree on the nature of the object's representation in the cortex.

Since the pioneering work of Nobel laureates D. Hubel and T. Wiesel (Hubel & Wiesel, 1968), it is well established that cortical neurons can perform operations that earlier level neurons cannot. In particular, most individual cortical neurons are sensitive to the orientation of the object's contours: a cell excited by a vertical contour will remain silent when seeing a horizontal contour, and vice-versa. The orientation selectivity of cortical neurons is thought to be crucial for the perception of form, a very important cue for object identification. In the cortex, the object's colour is not represented solely by the two distinct channels (red-green and blue-yellow) described above, but by a population of cells with a homogeneous distribution of preferred colors. An obvious question is to determine whether the same cortical neurons signal simultaneously the orientation of the contours and the object's colour, or whether these tasks are carried out by different populations of cortical neurons. Surprisingly, this simple question has been the matter of intense debate in the last decades.

On the one hand, a number of researchers reported that colour selective cells in primate V1 are not orientation selective, and vice-versa (Livingstone & Hubel, 1988; Shipp & Zeki, 2002). Furthermore, these reports proposed that colour selective, unoriented cells are found in clusters, corresponding to patches of tissue that stain for the mitochondrial enzyme cytochrome oxidase (CO), the so-called CO-blobs. According to that scheme, information about colour and orientation remains segregated within V1, and through most of extrastriate cortex as well. This scheme implies the existence of a later processing stage in which information about an object's visual attributes converge to yield a coherent, unified percept. The 'segregated' scheme has received indirect support from the discovery of functional streams in extrastriate cortical visual areas, with one stream responsible for object localization (the 'where' stream), the other concerned with object identification (the 'what' stream) (Ungerleider & Mishkin, 1982). The functional distinction between cells within and without the V1 CO-blobs is thought to be maintained in the extrastriate functional streams. Some results are at odd with this proposal.

Quantitative studies of V1 receptive field properties failed to find a segregation of function between cells within and without the CO-blobs. They found many V1 cells selective for both colour and orientation, and little correspondence between their distribution within V1 and the location of the CO-blobs (Leventhal et al. 1995. Similarly, in V2, the original proposal that color and form are treated by segregated neuronal populations, also corresponding to distinct CO-compartments, has also been challenged (Gegenfurtner et al. 1996). Many reasons have been invoked to account for these discrepancies. They imply the following requirements for any study that aims at resolving this issue.

Clearly, any conclusion drawn from data obtained on small samples of neurons will not be conclusive. A large sample of V1 and V2 cells is necessary to resolve the issue. Furthermore, functional properties of

cells are best assessed in an awake animal, because anesthesia can alter the response properties of neurons, particularly in extrastriate cortex. Finally, quantitative methods must be used to measure the cells' properties and classify them into functional classes. Qualitative classification of cells is difficult even for experienced researchers, and has proven quite unreliable. These conditions were all met by a recent study by Friedman et al. (2003). They recorded the activity of cells in awake, behaving monkeys, and used quantitative methods to characterize each cell. They collected data from a large number of V1 (425) and V2 (417) neurons. They computed indices to quantify each cell's selectivity for colour and orientation and studied the correlation between these indices. If colour and orientation were treated by independent, distinct populations of neurons, one should observe a negative correlation between selectivity for color and orientation. Their results clearly show that no such correlation exists for any of the indices they used. Their results demonstrate that many colour selective cells are orientation selective, and that non-oriented cells can also be unselective for colour.

These results demonstrate that the physical attributes of an object are not always treated by distinct neuronal populations. Instead, visual neurons are concerned by the features most useful to detect and identify objects in a natural environment. Object borders are important such features and they are, in most normal conditions, defined simultaneously by both a luminance and a color gradient. It is therefore not surprising that the primate visual system evolved neurons specialized for the detection of borders simultaneously defined by these two attributes. These results add to the growing literature showing that the properties of natural images determine the receptive field properties of visual neurons to a large extent. In other words, the lesson for neuroscientists is that to understand the brain, one should focus on the tasks that the brain has to solve, and not solely on the physical attributes of the stimuli used in the laboratory.

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Images of physiology

To launch a new series of physiological pictures, Thelma Lovick suggests images which might reflect our discipline in its broadest sense

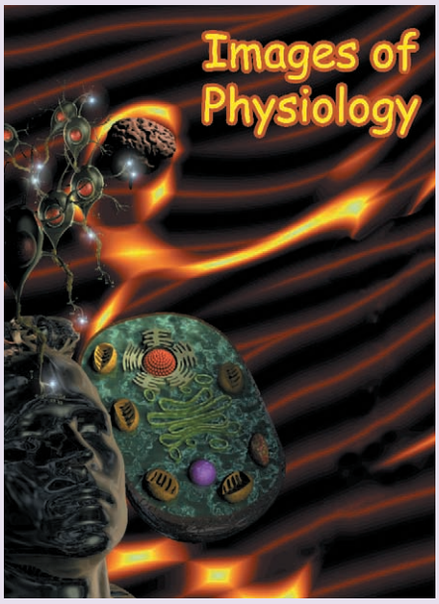


Image design: Terry Bambrook

Physiology can be viewed from many perspectives: think of the beauty of an attractive hypothesis backed up by elegant experiments and presented in a lucid manner from the lecture theatre podium by a master. Cringe at the tortured writings of an undergraduate doomed never to grasp fully the subject. Re-live the long hours in the lab that sometimes culminate in a real advance but so often lead to frustration as equipment fails or that brilliant idea just didn't turn out to be quite that good in practice.

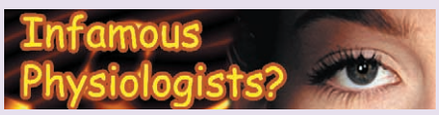
Then there are the physiologists themselves. Some are truly inspirational, others are downright boring but most are good in parts. We all have something to contribute. Then there is the perception of physiologists by the general public: as boffins in white coats, deranged torturers of animals or, just possibly, scientists dedicated to understanding how the body works and what goes wrong if it malfunctions.

Images of Physiology is a new feature for *Physiology News* in which we hope to reflect our discipline in its broadest sense and largely in image form

Send us your images of physiology!

The net will be cast widely. And we need your help. So if you have a stunning confocal image or original trace, let us show it! If you have a photo of an eminent physiologist from bygone years that might be of interest, or even one from the present day, we'd like that too. When out of the lab, some physiologists do the most amazing things - for example see the lady physiologists below! If you have made an ingenious bit of kit or you've found something intriguing in the back of a cupboard and you don't know what it does, let us see it. It's all about sharing your experiences!

Send your images for inclusion, ideas etc and comments on this feature to the Physiology News editorial office or email the Executive Editor at lrimmer@physoc.org or Thelma Lovick at t.a.lovick@bham.ac.uk



Do you recognise these lady physiologists (below), captured here outside their normal laboratory environment? Prizes go to the first three readers to submit correct answers to the Executive Editor: lrimmer@physoc.org

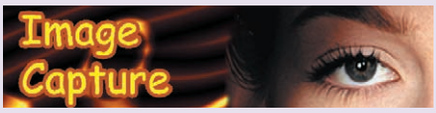
Impact factor: scary

I.M. Sechenov (1829-1905)

A visionary Russian scientist, Ivan M. Sechenov was one of the first physiologists to tackle the nature of 'psychical' activity. He asserted that the brain, like other organs, was governed by physiological laws and could be subjected to objective experimental analysis. He proposed that the principal forms of psychological processes could be regarded as reflex events, in the broadest sense. His revolutionary and highly controversial thesis was, after some difficulty, published in Meditsinsky Vestnik in1863 under the title *Reflexes of the Brain*. Its original title *An attempt to establish the Physiological Basis of Psychical Processes* had previously been rejected by the censor.

A contemporary of Darwin and an inspiration to Pavlov, Sechenov deserves more recognition by Western physiologists. The English translation of his book, published in 1965 by the MIT Press, is still worth a read today.

Impact factor: inspirational

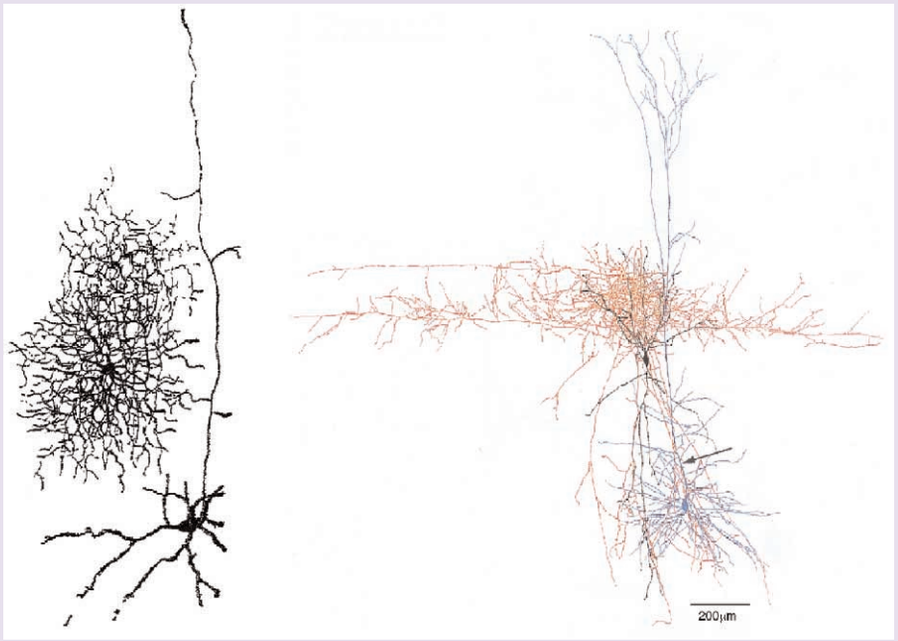


The camera lucida

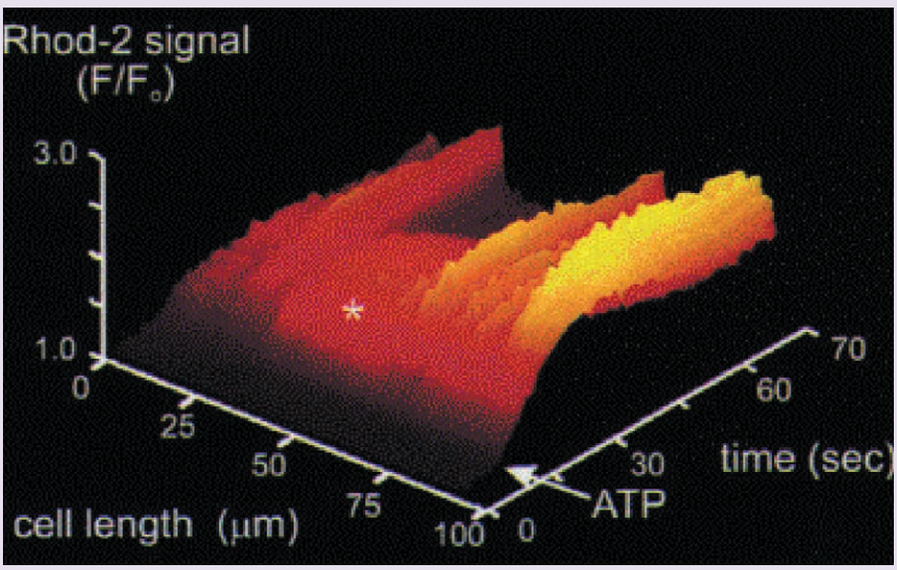
One of those great British inventions, the camera lucida was invented in 1807 by Dr Wiliam Wollaston as an aid to drawing for artists. But strapped to a microscope, this simple little gadget was soon taken up by physiologists and anatomists and for the first time, enabled them to produce high quality permanent images of objects viewed down the microscope. Nearly 200 years later, camera lucida remains a useful tool. It is still used for example, by neurophysiologists to reveal the morphological characteristics of neurones whose functional electrophysiological properties have been characterised by intracellular recording techniques.

The beauty of it: so simple, never breaks down and running costs are unimaginably low - requires pencil and paper only.

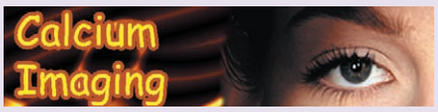
Impact factor: 10/10



Left: Golgi-stained cells in lamina IV of the motor cortex as seen by Ramon y Cajal. Right: Almost 100 years later a not dissimilar image of a pair of cortical neurones visualised after filling with biocytin. Dual intracellular recordings from this pair indicated that the interneurone (soma and dendrites in black and axonal arbour in red) was coupled to the pyramidal neurone (soma and dendrites in blue, axon not shown) via a single synaptic connection (arrow), which was revealed in the EM. From Thomson et al (1996). *J Physiol* **496**, 81 - 102



Evolution of calcium signal in cortical astrocytes loaded with rhod-2 in response to stimulation with ATP. Intensity profile along a line selected along the axis of a cell is displayed as a surface plot. A relatively fast and transient increase in [Ca++] in over the nucleus (*) contrasts with the slower and sustained widespread ncrease which develops over the mitochondria as the signal spreads. Image from Duchen (1999) J Physiol 516, 1-17



Where would we be today without fluorescent calcium sensitive dyes? Arguably the most powerful tool available for probing the kinetics of intracellular ion movement, many stunning and aesthetically pleasing images have been generated. But perhaps one of the most intellectually satisfying aspects of calcium imaging, thanks to advances in confocal microscope technology and image analysis software (see left), is the ability to portray calcium movements in time and space, bringing a new dimension to understanding intracellular and intercellular signalling processes.

Impact factor: picture worth a thousand words

The art of scientific endeavour

Keri Page visits Four Plus: Writing DNA, part of the Wellcome Trust's DNA50 celebrations

Keri Page

As scientists we take great pains to be objective, detached and unwavering in our dedication to Popperian falsifiability. For artists, the opposite is true. When a masterpiece is created in passion and doused in personal projection, there need not be one truth, and work is open to interpretation. While science is designed to be devoid of human contamination, art is the very epitome of the opposite ingredient, and may be an extension of oneself. Together one might expect these two opposites would mix like oil and water, but this does not appear to be the case.

Indeed, it seems we share a common drive: to describe our world and increase our understanding as best we know how. A fusion of art and science may not be commensalism, but a fresh symbiosis, in which science is infected with inspiration, awareness and hedonism, and art with new images and the taste of a dissimilar psychology. Certainly this collaboration is encouraged by the Wellcome Trust and flaunted in their most recent exhibition, Four Plus: Writing DNA, which is part of the Trust's DNA50 celebrations.

Displaying the work of 10 varied artists, the exhibition explores not only images of DNA but the lives of those historic figures who were integral to its elucidation, the process of research and discovery, and also the implications of this molecule for how people today see 'life.'

The use of unusual media is common to many of the exhibits. *The Secret of Life* by Jessica Curry and Dan Pinchbeck, for example, is a multi-sensory DNA-inspired sculpture (Fig. 1). Complete with 'music' that is apparently dictated by the rules that govern DNA coding. This audio visual experience centres around a white model, onto which Rosalind Franklin's X-ray diffraction photographs and portrait are projected. Like the complexity of the music, the shape of the sculpture is elusive. Because of its large size and close proximity, the shape cannot be fully appreciated, except from above - an intentionally awkward position from which to view the display. All together, these absurdities make one realise how palpable the discovery must have felt to Franklin – so close and yet so far.

In this way the exhibition speaks truths, not only about the discovery of DNA but also about the nature of the scientific research process as a whole. This sentiment is echoed by Richard Dedomenici's tribute to Franklin, '*The Rosalind Project.*' A combination of video and a hand-scribbled diary of sorts, the piece draws links between Franklin's career path, her crystallography and the process of innovation. The nonsensical detail and tortuous description of the artist's 'journey', however, hints of the mundane repetition that pervades the lives of practising research scientists.

The full exhibition is spread over five floors, and across two Wellcome buildings. With map in hand I negotiated the maze of exhibits, only to find that by the end, not only had I developed a headache but I had traversed five floors, in a helical fashion, in search of titbits. Imitating the flavour of discovery, the excursion was far from a walk in the park.

Some of the Four Plus: Writing DNA exhibition features the archives of Francis Crick. Purchased by the Wellcome Library in 2001, the papers will soon be fully accessible to library users. A sketch drawn by Crick himself shows the way the image of DNA was initially conceived (Fig. 2).

Figure 1. Jesicca Curry and Dan Pinchbeck. The Secret of Life 2003.
Mixed media installation with perspex, digital sound, animation and video projection. Dimensions variable

Reassuringly human and abstract, the drawings, in combination with annotated manuscripts of the original *Nature* paper of 25 April 1953, make the discovery of DNA feel remarkably more tangible and fallible. This personal touch is cemented by Penny McCarthy's drawing of the Watson and Crick paper. The painstaking effort and concentration that would have been required to create this pencil drawn replica – of actual size, in some way mimics the hard work behind the print. For information about the other works at the exhibition and the artists involved see: www.wellcome.ac.uk/en/1/awtprerel0103n281.html

An amalgamation of art and science can obviously be entertaining, but how does each side of the engagement benefit? The Wellcome Trust's TwoTen Gallery was established in 1995 with the main aim of engaging public interest in science. 'In order to raise awareness of medical, ethical and social implications of biomedical science, one of our strategies is to use the mechanisms of engagement via the visual, literary and performing arts,' says Denna Jones, Curator at the Wellcome TwoTen Gallery. The gallery puts on several exhibitions a year simply to 'explore the possibilities' of sci-art, says Jones. Public understanding is something science desperately needs. Perhaps we should embrace the emotive and aesthetic side of science in order to help ourselves.

The Wellcome Trust further facilitates scientific art in their schemes and competitions. As well as commissioning two six-month artist residencies a year, the Trust annually runs a *sciart* award scheme. This scheme invested £1million in art-science projects in 2002 alone (Website). A competition for amateur photographers, run by both the Wellcome Trust and BBC, is also currently underway – deadline 30 June, 2003. Entitled '*Imagine*' the competition invites photographs

Figure 2. Francis Crick, sketch (pencil) of double helix (1953)

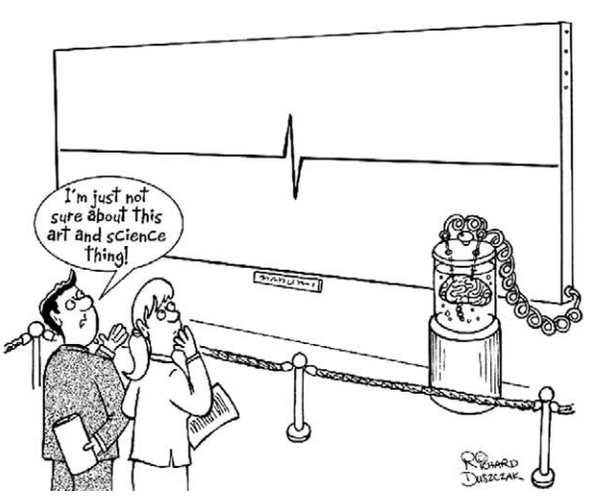
inspired by DNA, genetics or heredity.

Self-indulgence is unlikely to be the only outcome of science-inspired art for researchers. We might also see the emergence of art-inspired science. Since artistic interpretation is a product of a self-awareness and psychological complexity unique to our species, new lines of scientific enquiry might be drawn from looking more intimately at artworks. Benefits have already been drawn from closer scrutiny of how self-portraits are affected by developing Alzheimer's (William Utermohlen), how amputees visualise their phantom limbs (Alexa Wright), of hand-eye co-ordination during portrait drawing (Humphrey Ocean and John Tchalenko), and how motor control in choreography is influenced by zero gravity (Kitsou Dubois and Imperial College Biodynamics Group). These are just a few of the developments born of the Wellcome Trust's past competitions and exhibitions. Perhaps together scientists and artists might continue to explore the space between these two disciplines.

Scientists themselves, however, are not without their own sense of aesthetic beauty. Contemporary science provides us with fabulous new tools and imaging techniques, capable of telling complex stories about biology. Visualising cutting edge concepts about our world and our bodies in this way is increasingly viewed as having artistic merit. If you are feeling creative or are proud of an image you have created that reflects our discipline, why not jump on the science-art bandwagon and submit your ideas to Images of physiology (see p. 21).Who knows where this new kind of experimentation will take us?

Keri Page
Department of Zoology
University of Cambridge

Four Plus: Writing DNA continues at the TwoTen Gallery and the Wellcome Building, London, until 29 August 2003.



The outback experience

Dear Editor,
In Ashmore's very amusing account of his visit to Oz (*Physiology News*, number 51) he makes the statement that the celebrated photograph of Eccles, Katz and Kuffler (reproduced in *From Neuron to Brain*) was taken in the main quadrangle of Sydney University, according to Max Bennett. This photograph was taken in Martin Place in the heart of Sydney. Martin Place is the site of the Cenotaph and so corresponds to Whitehall in London. It is now closed to vehicular traffic but in 1941, when the photograph was taken, you can see cars parked on both sides of the road and the old General Post Office in the background. The trio are walking uphill towards their laboratory in the Kanematsu Institute in Sydney Hospital. It is believed that they had come from Sydney University where one of them (probably Eccles) had given a lecture (on the endplate potential?). In those days it was customary for commercial photographers to take shots of passers-by at random and hand them a card with a reference number on it. Anyone who was interested could check the photo later and purchase it if they liked it. The anonymous photographer who took this photo probably never realized how famous his shot had become. Max Bennett assures me he did not give any dud information to Ashmore. It is reasonable to conclude that either one or both of them had been over-indulging in the fermented grape juice which is so popular with Poms down under.

Liam Burke
Emeritus Professor of Physiology
University of Sydney, Australia

Jonathan Ashmore replies:

Many thanks for the correction about the EKK photo in my lightweight article in *Physiology News*. The facts are much more interesting than fiction. Of course, had I done my research properly, I should have realised that the cars in the photo could not possibly have been in the University of Sydney.

I hope you will mollify Max who certainly did not give me dud information - I remember him gesturing in the direction of the quad while telling me the story. That was the day before going to Martin Place as a tourist so the connection escaped me.

As I recall, the closest we got to fermented grape juice was a flat white in a paper cup which I promptly spilt down my trousers. Perhaps Max did slip in some centrally acting factor after all.

Abstracts – to be or not to be?

Dear Editor,
In *Physiology News*, number 51, Ann Silver writes about Abstracts. Unfortunately, unlike her I do not have a long series of copies of the Society's magazine since I have not received them for many years. What Ann Silver writes about abstracts makes a great deal of sense.

In particular the loss of pre-circulation of programmes seems to me to be a mistake. I do know about the internet address but the Society, in common with so many other organisations, is throwing the onus and the cost onto their customers or members. This may matter little to members who are employed in universities and institutes since the costs of computer usage are hidden to them personally. That is to say purchase of a computer, rental of telephone line, subscription to an ISP, printing costs including ink cartridges, and paper, and so on. This means that the retired members who pay for all these things themselves are those that are penalised. There could be a view that this does not matter since they are unlikely to be active nor to contribute much to discussion at meetings. But the effect is to tend to exclude them even if they wish to stay a part of the Society and so to lose their experience of science, of life, and of their willingness to ask simple questions.

I do not know what the Society now does about ensuring that Chair-men/women of sessions have the abstracts well beforehand, maybe they also are expected to download them, but do they? This is important because Chair-men/women of sessions should certainly have read the communications carefully beforehand. It is their role to supervise the smooth running of the session, keep the speakers to time, direct questions to the speaker, identify the person asking the question, and most of all to enliven and stimulate discussion. They cannot carry out this last task if they have not read the papers beforehand and so will find it difficult to engage the audience.

This last point, engagement of the audience, is often not uppermost in the minds of the presenters at the recent meetings I have attended. Far too often there is an extraordinarily bizarre use of colour simply because Microsoft have made it available, not because colour helps to convey information. Coupled with that is the imposition on the audience of far too many slides. In a two or three hour session it is quite impossible to take in 10 slides every 15 minutes, especially when the axes are not defined nor are the units given by the speaker and the histograms change colour without warning. The blame for this retrogressive behaviour must lie with supervisors who do not train their graduate students and post-docs to discipline themselves. All this means that the speakers are talking to themselves or maybe one or two friends whilst other members of the Society are not engaged. Do the speakers practice their communication in front of members of their department who are not working in their group ?

A failure to communicate clearly is a pity, for some people go to meetings in order to learn about fields new to them. In addition those who produce these awful communications will not endear themselves to members of the Society who may have jobs to offer.

Tim Biscoe
Emeritus Professor of Physiology
University College London

Review of Society grants

New grant schemes for Members and Affiliates

As of 1 August, 2003 the Dale and Rushton Scheme, International Bursaries and International Meeting Travel Grants will be consolidated to form one grant for Members, and the Affiliate Travel Scheme, Affiliate Home Meetings Scheme, International Bursaries and International Meeting Travel Grant will be consolidated to form one grant for Affiliates. There is now one form available for Members and one for Affiliates, which can be accessed from the website. Criteria and eligibility are also published on the web. Members and Affiliates are invited to apply for money to attend and present at scientific conferences (including domestic and international Physiological Society meetings, sponsored meetings and symposia, meetings of other societies), to visit another laboratory for collaborative research or to acquire new techniques or to attend a practical workshop or training course. Guidelines and scoring criteria are published below.

These changes have resulted from a review of Society charitable expenditure, conducted in 2002. The aim was not to reduce spend, in fact it is hoped that it will increase with the larger income stream owing to the change of publisher. However, there were some inconsistencies with the schemes that had evolved, and also a feeling that streamlining administration would be helpful.

Academic life has changed over the last few years, and the Society's membership has altered in response. Owing to greater use of the web and email, scientists increasingly collaborate with colleagues in far flung places. There is a greater need for scientists to move around the globe for collaborative visits and meetings. There is also an expectation that Society meetings will have a truly international flavour, and that there is a need to support scientists from developing countries to attend our meetings.

The original grant schemes were developed based on the premise that most of our Members and Affiliates lived and worked in the UK and Republic of Ireland, and would require money to travel overseas. When a need for funding was recognised which was not in the remit of existing schemes, new schemes were introduced. It is envisaged that by consolidating the schemes, there will be greater transparency (all applications will be viewed side by side), and also that no Member will be disadvantaged purely on the grounds of where they live. Priority in all cases will be given to Members/Affiliates applying for funds to attend Physiological Society meetings, workshops or sponsored events.

There are new two monthly deadlines for receipt of applications (published on p. 27). Please note that applications cannot be considered retrospectively. Deadlines will always be published on the website.

A final plea from the office. We try to transfer as much money as possible by BACS transfer. The most common reason for delay in paying grants is incorrect bank details. Please double check that the account numbers, etc. submitted are correct.

The new schemes will be trialled for one year, and then reviewed. For questions concerning the review please contact myself or Jamie Gould at the office.

Maggie Leggett

Members Grant Applications

Scoring criteria

1. Active membership, or applicant in the process of applying
2. Benefit to applicant (development of research, career progression, opportunities for collaboration and networking)
3. Benefit to physiology
4. Benefit to Society
5. Other funding opportunities (including applications to other appropriate sources)
6. Breakdown of costs

Guidelines

1. Members are invited to apply for travel grants:
   a) to attend and present* at a scientific conference (including domestic and international Physiological Society meetings, sponsored meetings and symposia, meetings of other societies and other international scientific meetings relevant to physiology). A copy of the abstract should be included.
   b) to visit another laboratory for collaborative research or to acquire new techniques
   c) to attend a practical workshop or training course.
2. Applications from Members not resident in the UK/Republic of Ireland to present at meetings of other societies, or for collaborative visits outside the UK and RoI, may be considered under exceptional circumstances.
3. Applications must be made before the intended travel date; retrospective applications will not be considered.
4. If you are in the process of applying for Membership, please include your address and date of application in a covering letter, together with a covering letter or email from a sponsor, preferably a current Member of the Society or your Head of Department.
5. Scoring criteria are published on our website. Looking at these might help you to make a successful application.
6. Please note that normally you will be eligible for one grant a year, up to the value of £600, although more may be available for lab visits and courses.
7. If you have any questions relating to the grant or membership application process, please contact Jamie Gould at: jgould@physoc.org, telephone +44 (0)20 7269 5726.

* Presentations include invited lectures, oral and poster communications, or demonstrations.

Affiliate Grant Applications

Scoring criteria

1. Active Affiliate membership, or applicant in the process of applying
2. Benefit to applicant (development of research, career progression, opportunities for collaboration and networkin
3. Benefit to physiology
4. Benefit to the Society
5. Other funding opportunities (including applications to other appropriate sources)
6. Testimonial/letter of support from supervisor/Head of Department
7. If UK or RoI resident applying for overseas travel - evidence of presentation at a domestic meeting of the Society

Guidelines

1. Affiliates are invited to apply for travel grants
   a) to attend and present* at a scientific conference (including domestic and international meetings of the Physiological Society, meetings and symposia sponsored by the Society, meetings of other societies and other international scientific meetings relevant to physiology). Please include a copy of the abstract. Please note that the grant will not be awarded unless you are the presenting author.
   b) to visit another laboratory for collaborative research or to acquire new techniques
   c) to attend a practical workshop or training course.
2. Applications from Affiliates not resident in the UK/Republic of Ireland to present at meetings of other societies, or for collaborative visits outside the UK and Eire, may be considered under exceptional circumstances.
3. Applications must be made before the intended travel date; retrospective applications will not be considered.
4. Please note that in order to apply for travel expenses to non-Society meetings overseas, you should have presented* at a domestic Physiological Society meeting. Please include full details on the application form.
5. If you are in the process of applying for Affiliate Membership, please include your address and date of application in a covering letter.
6. Please include a covering letter or email from a sponsor, your supervisor or Head of Department, preferably a Member of the Society.
7. Scoring criteria are published on our website. Looking at these might help you to make a successful application.
8. Please note that normally you will be eligible for one grant a year, up to the value of £400, although more may be available for lab visits and courses.
9. If you have any questions relating to the grant or membership application process, please contact Jamie Gould at: jgould@physoc.org, telephone +44 (0)20 7269 5726.

* Presentations include oral and poster communications, or demonstrations.

Grant Deadlines

Affiliates (includes any applications from members wishing to apply for funds to go to the relevant Society meeting)	Members
31 August, 2003 (Cambridge)	30 September, 2003
31 October, 2003	30 November, 2003
31 December, 2003 (Glasgow)	31 January, 2004
29 February, 2004 (Cambridge)	31 March, 2004
30 April, 2004 (Cardiff)	31 May, 2004
30 June, 2004 (Cork)	31 July, 2004
31 August, 2004 (King's)	30 September, 2004
31 October, 2004	30 November, 2004
31 December, 2004	

Biosciences Federation

The Federation has had an active first few months. Recruiting members and fund raising have been key, and significant advances have been made in both areas. Replies to consultation documents on subjects such as the Higher Education White Paper, the Forward Investment Strategy of the MRC and teacher professionalism and the role of subject specialism have all been submitted.

Until the Federation achieves a firm financial footing, it must rely on staff seconded from various societies to provide a secretariat. Hence in the policy area there has been much activity, thanks to the excellent work of Mike Withnall (Biochemical Society) and latterly Catherine Joynson (Institute of Biology). In April, the Physiological Society Executive Committee took the decision to second me one day a week for a year to assist in the areas of public relations and education. One of the activities I have been involved in is the organisation of the Federation's first event, an Education Colloquium, to be held on 6 October, 2003 in London.

Increasingly, when speaking to Members, concerns are expressed regarding the levels of knowledge of their undergraduates when they arrive at university. Changes in post-16 qualifications mean that universities are accepting students with a broader range of AS and A2 levels. Unfortunately, in order to achieve that extra breath, some depth has been lost. In addition to this, many institutions are still facing recruitment problems and need to know how best to attract students and how to help them overcome obstacles when they arrive. This colloquium will explore some of these issues, bringing together academics, teachers, and those that have conducted research in the area. The colloquium is free and we would welcome any interested Member who wishes to attend. The programme and registration form can be found on the education page of the website (www.bsf.ac.uk), where further details of current Federation activities are also available.

Maggie Leggett

Hot Topics

The 6th CHOP 'Hot Topics' meeting held in Manchester on 24 – 25 March (co-hosted by Arthur Weston) was the first joint meeting of the Committees of Heads of Pharmacology and Physiology. And it was a timely meeting, with lots of discussion and debate about interdisciplinary work, addressing both political and scientific issues.

Professor Alan Cuthbert (Cambridge) provided a challenging start with a speech 'from the heart' asking us all to hold on to our names, guard our courses and increase our profile with the general public. Speaking as a member of both the Pharmacological and Physiological Societies, Alan Cuthbert was well placed to give a

BIOSCIENCES FEDERATION

Education Colloquium

In collaboration with the Learning and Teaching Support Network Centre for Bioscience

Changes and Challenges
The Changing Face of the Bioscience Undergraduate

- How can we attract the best students into science?
- How is the school science curriculum going to change?
- How will it affect the quality of our future science undergraduates?

Colloquium Topics

Government and its Perspectives on Science Teaching

Changes to School Science

New challenges faced by first year undergraduates

Student perception of university science courses

The link between universities and schools

We invite you to listen to talks and join in the discussion of these important issues at

Hamilton House (NUT HQ):
Mabledon Place,
London WC1H 9BD on

Monday 6th October 2003

Registration and coffee at 10am
Lunch and refreshments will be provided. Wine reception at 4.30pm

This Colloquium is FREE.

For further information and to register online see www.bsf.ac.uk Closing date: 30th September, places are limited.

INSTITUTE OF BIOLOGY

ltsn Learning and Teaching Support Network

British Society for immunology advancing science

SEB

Society for general Microbiology

The Physiological Society

perspective on the government white paper and to raise concerns which this clearly signalled for our future. In a world of new challenge for education, from widening participation to top up fees, and new challenges for science around new technologies, from genomics to proteomics, we needed to be attentive to our departments. Alan Cuthbert questioned the level of investment in new technologies – rather than leading to any enhanced drug discovery programme, the massive financial investment in the new technologies coincided with a massive reduction in the number of new drug candidates reaching the regulatory authorities. The pharmaceutical industry was calling for more hands-on skills, for employees with in vivo technical knowledge. So, time to re-think our research focus? Not surprisingly, the discussion continued well into the evening!

After such provocative debate, the following day could not have started better. Roberto Solari (former Head of Cell Biology at GlaxoWellcome) gave a complex and professional talk around the post-genomic era. The emphasis on interdisciplinary work was excellent, and set the scene for the remainder of the morning. But the talk also raised the issues of the previous evening. Pharmacologists and physiologists all recognised the rapid advances made in the fields of genomics and proteomics; the question for many was whether the advances (and the promises for the future) lived up to the enormous investment – person power and financial. No-one doubted the importance of the core science knowledge which had evolved but this needed strengthening to provide a firm basis for scientific advancement and drug development.

As Nancy Rothwell (Manchester) said, provided we work together to design studies with rigour then the outcomes can be maximised. Again and again the discussions of the first joint meeting of the Committee of Heads of Pharmacology and Physiology returned to the advantages of interdisciplinarity.

So to a talk which could have been controversial and political. Slick and professional, articulate and precise, Nancy Rothwell gave firm foundations to the formation of the Biosciences Federation. There was no controversy as to the main theme, to embrace and engage in an agenda for change, to grasp new opportunities, with a united voice – whilst maintaining our identities. This is not to say that emotions did not run high – but a 'coming together' is bound to create suspicions and heated debate.

The debating mood continued after lunch (fuelled by lots of lunchtime networking and discussions around RAE funding, university mergers, and visions for the future – all very therapeutic!).

The first topic of the afternoon was the future of animal-based research in the UK and how we should address the 3Rs. Armed with a complimentary copy of 'from guinea pig to computer mouse', delegates were ready for debate. Bob Coombes (FRAME) gave an elegant presentation on sensible ways to tackling the 3Rs and Clare Stanford (University College, London) gave us insight into public perceptions of what is or is not appropriate to develop as a medicine. There is no doubt that as professionals we need to rehearse our PR since the level of understanding of the public must be appreciated – we may see the medical benefits of anti-obesity drugs, the treatment of drug dependency withdrawal or the very positive uses for Viagra, but the public may see only the quality of life issues. 'Be prepared to defend the benefits of research' was the message from two highly committed speakers.

On to education per se, and the second debate of the afternoon. Should we, as educationalists, be taught to teach? The issue on debate was clear: 'This house believes that requiring all university teachers to have a teaching qualification will destroy the British University System'. To support the motion Ian Naylor (Bradford) gave a tour through the history of education, from Voltaire ('all styles are good except boring') to Memoir of a Thinking Radish by Peter Medewar (1986: 'A dialogue to promote, exercise and enlarge the powers of the mind'). Ian's support for the motion drew on personal experiences and concern for the product which entered HE from the School system. But does this mean we should not have formal pedagogical education?

Lorraine Stefani (Strathclyde) gave a powerful outline for the need to educate all academic staff in pedagogical issues, to help them to engage the new student mix in the learning process, to encourage the autonomous and independent learner, to create reflective learners (and teachers). Lorraine felt it was crucial to expose staff to the craft of teaching, to give emphasis to the scholarly pursuit of teaching. All the pedagogy required for any person committed to QA procedures was espoused by Lorraine, and the audience listened! So, on to the debate.

The pedagogical experts were harassed by those who were 'insulted' by Lorraine's comments that one needed to be taught the powers of reflection, different teaching styles, different assessment procedures. Kathy Kane (Strathclyde) brought calm to the storm by supporting Lorraine's logical pedagogical presentation and stance, but then outrage was expressed at the emphasis on 'requirement' for a teaching qualification. It was a fun debate on a difficult subject. Whilst the writer believes everyone in the room acknowledged the need for education of the teacher, the nature of the formality of this provision was the dividing query – and the motion

was carried – despite the chair for the afternoon, Ian McGrath (Glasgow) acknowledging that he was a convert to pedagogical education!!

Brian Furman (Chair, Committee of Heads of Pharmacology) chaired a pharmacological/physiological morning and Ian McGrath (Chair, Committee of Heads of Physiology) steered the afternoon debates. A truly interdisciplinary event which all agreed should be the start of further sharing and collaboration. The best possible way to face change and challenge ... together!!

Brenda Costall
Secretary, Committee of Heads of Pharmacology

SET for Britain

Poster presentations by Britain's top younger scientists, engineers and technologists at the House of Commons, 17 March, 2003

The 5th annual parliamentary presentation of British research and R&D concluded the events of this year's National Science Week. Two receptions were held. The first, at lunchtime, covered science, engineering, medicine and technology with a more specific theme of nanotechnology being shown at a separate reception in the evening. These events are held annually at the House of Commons and sponsored by GlaxoSmithKline. They aim to encourage dialogue between Members of Parliament and Britain's younger researchers.

These meetings also provided an opportunity for younger scientists to exhibit their current research and meet with their peers from a wide spectrum of science, medicine and technology. Some of the more topical subjects covered at the lunch-time reception included railway safety, urban air quality, biological weapon detection, military aircrew safety and the relationship between speed cameras and road traffic accident statistics.

Sponsorship from the Physiological Society enabled myself and two other affiliates to attend to represent the society. Our work was presented at a level accessible to non-scientists, which in itself was an unusual challenge and was well received by biologists and non-specialists alike.

Almost 100 MPs expressed interest in attending the receptions. Unfortunately, the timing of the event coincided with the final debate on the Iraq crisis but, nonetheless, a significant number of MPs did find the time to visit the exhibition despite more pressing political concerns. Though not the main objective concern of these events, discussion of funding and the future of UK science was inevitable - giving us the opportunity to raise concerns of the upcoming generation of scientists and engineers regarding funding, career prospects, research facilities and training, and above all, to discuss and hopefully influence government policies of commitment to research for the future. These topics are covered by the Commons' Select Committee for Science, as part of the 'Voice for the Future' initiative.

Overall this event was an interesting occasion, allowing direct interaction between younger researchers and MPs, promoting the value of researchers and their work for the future.

Lauren MacKenzie
The Babraham Institute

Careers conferences: where does your future lie?

At the end of each year the Physiological Society, along with other learned societies (Biochemical Society, British Pharmacological Society, British Society for Immunology, Institute of Biology, Society for Experimental Biology and Society for General Microbiology), take part in organising Life Science Careers' Conferences for undergraduate and postgraduate students.

This year the venues and dates are:

King's College, London
1 November, 2003

UMIST, Manchester
15 November, 2003

University of Cardiff
29 November, 2003

These conferences give students information about career opportunities available to them after graduating. They are the only careers' conferences targeted at life science students and are a must for any student unsure of what path to take. Topics covered throughout the day include: research in universities and in large companies, careers in clinical and biomedical science, teaching in schools, patent law, careers outside the laboratory, volunteer work abroad, job hunting and interviews, and science communication. We also hold *curriculum vitae* workshops which give delegates a chance to receive feedback on their current cv.

At each conference, many companies and universities are invited to take part in an exhibition. This gives the chance for undergraduates and postgraduates to meet employees from these companies and get an insight into the work they do.

Each conference attracts around 300 undergraduates and postgraduates from Universities and research institutes throughout the UK.

All undergraduate and postgraduate life scientists are welcome to attend, and find out where their future lies...

Sai Pathmanathan

WHERE DOES YOUR FUTURE LIE?

Are you a life sciences undergraduate or postgraduate student?

Do you want to learn about career opportunities in life science today?

If so don't miss out on the Life Sciences Careers Days:

1st November 2003 London

15th November 2003 Manchester

29th November 2003 Cardiff

Programme includes:

- Talks on R&D, science communication, postgraduate/postdoctoral opportunities, teaching, patent examination & much more
- Making applications
- CV checking service

Details of each event and booking forms are available on the web:

www.bsf.ac.uk/careers

All enquiries to:
Events Administrator
Sai Pathmanathan
The Physiological Society
PO Box 11319, London WC1V 6YB
Email: spathmanathan@physoc.org
Tel: 020 7269 5727

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Sixth Form Workshops: Bristol and Chester

March 10-16, 2003

CHESTER COLLEGE

BRISTOL

On the 12 March, 2003 two sixth form days sponsored by the Physiological Society took place in Bristol and Chester.

The Faculty of Applied Science in the University of the West of England held a practical hands-on workshop for A-level Science students called *THE BRAIN-JUST USE IT!* The event was part of Brain Awareness Week and National Science Week. Schools from all over the South West of England attended (with one school travelling all the way from Cornwall). At Chester College of Higher Education a set of Sport and Exercise Physiology workshops attracted students from all over the North West. Approximately 80 students turned up to each event, although many last minute applicants had to be turned down due to lack of space, resulting in teachers requesting that more such events should be held.

Each sixth form day consisted of a variety of lectures and workshops. Topics included: electron microscopy, nerve conduction, pupillary reflexes, optical illusions, animal models of stroke, enteric brains, the brain and exercise, stress biology, immunoassays, and even an advice session about applying to university.

Although the workshops were sponsored by the Physiological Society, much of the hard work and organisation was by Dr Stephen Gomez (Bristol) and Dr Graham Bonwick (Chester). They both did a terrific job of making sure everything ran smoothly, and that students were entertained and attentive. Thanks must go to all those who gave up their time to help run the events (Dave Patton, Carolyn Paul, Dave Lush, Priscilla Heard, Malcolm Watson, Roy Pope, Richard Osbourne, Stuart Bruce-Low, John Williams, Mary Cotterrell, Becky Kendall, and Sarah Andrew).

Feedback from both workshops has been extremely positive with requests to run additional events. It was encouraging to see so many students take part in the workshops and the teachers were able to see students apply their knowledge to top level research and ask intelligent questions.

Many students who have attended sixth form days in the past have progressed to study physiology or a related subject at university. For many of them these sixth form days were their first chance at seeing real science in real laboratories. This is a very powerful form of advertising for the universities who organise the event, as well as better establishing their links with local schools.

Anyone wishing to organise a sixth form day next year, please contact: me on 020 7269 5727 (spathmanathan@physoc.org).

Sai Pathmanathan

Getting on your nerves! Nerve conduction practical where students measured the conduction velocity of the ulnar nerve

Free CDs

A generous grant from Pfizer has enabled the Physiological Society and the British Pharmacological Society to offer departments of pharmacology and physiology a free CD about laboratory animal anaesthesia, surgery and peri-operative care. These CDs are produced by the University of Newcastle. The CDs have been reviewed by one of our Members, who commended them and commented 'They can be used to illustrate specific aspects of anaesthesia and operative techniques, and to supplement other material. The material covered is appropriate for anyone planning to start to carry out experiments on anaesthetised animals, and also for scientists with experience in such experiments who may need a quick update on current methods.'

If you would like to receive a copy, please contact Sarah-Jane Stagg at the BPS Office (sjs@bps.ac.uk). Supplies are limited, so copies will be distributed on a first come first served basis.

Maggie Leggett

Safety farce

Here in the Cain laboratory we have just been subjected to that annual joy, the safety inspection. The safety inspection is one of those occasions when you find out just how many friends you do – or don't - have in the department.

If they want to give you a pass, they can, by ignoring the odd dangling power lead, the computer with no side panels, the heavy objects on high shelves (where the hell else are you supposed to store anything?) and the bottle of glass-cleaning stuff that's lost its label. (Danger! Alkaline Hazard! Irritant!).

Provided that (i) they don't find the bottle of whisky you stashed behind the Qiagen catalogue, and (ii) you don't have an incriminating week-old Tandoori chicken sandwich in the fridge, you can usually just about get away with other stuff. But if they want to bust you, they can.

It's a bit like traffic wardens. Remember parking on that single yellow line at precisely 6.32 p.m., a full two minutes after it was legal? And then the traffic warden ticketing you, because their watch said it was 6.29 p.m.? (Of course, a smart traffic warden is bound to have a watch that runs two or three minutes slow. Makes sense.) Anyway, you ended up with a ticket. Which you had to pay.

The point being: you can't beat them. They can always get you if they want to.

And it's the same with the safety people. There are enough rules that they can always find you contravening at least a few of them. The question is whether they decide to enforce them all that particular day.

So you had better pray that your Departmental Safety Officer is a reasonably normal human being. And not a rule-crazy zealot, or a person who missed his or her true calling as – what else - a traffic warden.

Of course, those who are really to blame are the civil servants and legislators who made University laboratories subject to safety regulations, most of which were clearly designed for industrial workplaces occupied by people with less common sense than the average potted plant.

Because, let's face it, most of the rules are completely mad. For instance, although one no longer has to fill in a COSHH assessment for every chemical (which led originally to such Kafka-esque classics as the COSHH assessment for sodium chloride) one still fills them in for ANY chemical deemed an "Irritant". This includes such high-risk substances as calcium chloride, potassium chloride, and glycerol.

Of course, one should always treat poisonous substances with respect, and very poisonous ones with more respect still. But for everything else, not eating it or rubbing it in your eyes (common sense) is pretty much enough.

After all, eating my dodgy chicken sandwich and its payload of *Campylobacter* will probably make you a lot sicker than accidentally inhaling a bit of acetone.

Unfortunately, the fact that about half the chemicals on the shelf still have a COSHH sheet tends to blur the distinctions between them, even when the distinctions are important. So the safety bureaucracy actually ends up making things less safe.

Or take most of the GM Rules. Do these really concentrate on the few things that are actually likely to be hazardous? I don't think so.

Instead, they just create work. All cell culture waste has to be treated as a Biohazard and autoclaved, in some cases twice, before it can be burned. Every pipette tip, every plastic tube, every pair of gloves. Even the effluent perfusate from your patch-clamp rig.

In the old days this waste perfusate went down the sink. We would mix it with bleach first to keep the lab fragrant and hygienic, especially if we had been doing an experiment with something toxic. Very conscientious, I used to think.

But nowadays doing this is a no-no. Why? Because – shock horror - human cells might get into the waste water system.

Well, perhaps it has escaped the notice of the law-makers, but human cells go into the waste water system every time a human being does what comes naturally and answers the call of nature. Remember your excretory physiology? The main pathways for daily iron loss from the body are ... yup, that's right.

The difference is, in a lab we have to have a specially sealed floor, and the waste goes for autoclaving. In your bathroom, you just flush.

If only one could just flush most of the safety bureaucracy. But no doubt it's here to stay. Along with all the rest of the tons of regulatory paperwork that is slowly drowning the public sector in Britain.

As a final aside, here is a little Safety Cautionary Tale. A couple of months ago I spent 10 minutes writing out a COSHH form for 30% Hydrogen Peroxide. Oxidizing! Causes burns! Hazard!

Clearly highly lethal stuff, only available to qualified scientists for use under the most carefully controlled laboratory conditions.

Or alternatively: available in litre quantities in your local supermarket, where it sells as "Biodegradable Chlorine-Free Bleach".

Don't worry though. It has a hazard sign on the label. It's just that no-one know what it means. Except for us scientists.

Mark Cain

Bernard Katz

1911–2003

1911	Born, 26 March, Leipzig, Germany
1920	School – König Albert Gymnasium, Leipzig
1929	First preclinical work, University of Leipzig
1931	Preclinical exams
1931	Undergraduate work/physiological research with Martin Gildemeister
1933	Siegfried Garten prize
1934	MD degree, University of Leipzig
1935	Short period working at Leipzig Hospital, followed by arrival at UCL
1936	First publication with A.V. Hill in *Proceedings of the Royal Society*
1939/45	Australia, working with John Eccles and Stephen Kuffler
1941	Became a naturalised British citizen
1942/43	Pilot Officer Bernard Katz, Royal Australian Air Force
1945	Married Marguerite (Rita) Penly
1946	Returned to UCL as Assistant Director of Research, Biophysics Research Unit
1950	Appointed Reader in Physiology
1952	Professor of Biophysics and Head of Department, UCL
	Fellow of the Royal Society
1957/63	Editor, *The Journal of Physiology*. Chairman 1961 - 1963
1967	Copley Medal of the Royal Society
1968	Fellow, Royal Society of Physicians
1969	Knighted
	Foreign Associate, American Academy of Arts and Sciences
1970	Awarded Nobel Prize, jointly with Ulf von Euler and Julius Axelrod
1976	National Academy of Sciences (USA)
1978	Retired as Head of Biophysics Department, UCL
1982	Awarded Orden Pour le mérite für Wissenschaften und Künste
1990	Ralph W. Gerard Prize, Society for Neuroscience
	Honorary doctorate, University of Leipzig
1999	Rita Katz died
2000	Unveiling of BronzeTafel at the University of Leipzig
2003	Died, 20 April

In science, it is no bad thing to have heroes. True, there are some people who resent anyone cleverer than themselves, but personally I like them. I won't embarrass those of my heroes who are still alive by naming them (especially those who are younger than me), but I can safely say that Bernard Katz was one of them, along with his mentor A.V. Hill.

In the preamble to his inaugural lecture, given in 1952 when he became professor of Biophysics at UCL, Katz expressed his gratitude to A. V. Hill 'for all I have learnt, not only as a pupil of a great master of experimental research, but by having served my apprenticeship with a man who never, under any circumstances, allows the deceptive counsels of human vanity to enter into your argument –with a man whose one inflexible purpose has always been the pursuit and acknowledgement of truth'. It is very clear that BK learnt well from his own hero, because these words could serve as well to describe his own values as they described Hill's. That, as well as his science, was why he was an iconic figure for a whole generation of post-war physiologists and pharmacologists.

Bernard Katz was one of the last of the generation of distinguished physiologists who were refugees from the Third Reich and who contributed immeasurably to the scientific reputation of their adopted country. Like many others (Feldberg, Schild, Blaschko and Vogt, to name but four), BK's German accent never entirely disappeared. It seemed that through most of my scientific lifetime the most distinguished of my seniors mostly spoke with guttural accents (I remember my own boss, Heinz Schild, a kind and gentle man, announcing in a strong accent that he had been to a party and was the only English person there). It was a continuous, and salutary, reminder of the follies of the 20th century, and of the far harder time that these people had than we do now. Science may have become less gentlemanly, and funds may be short, but we do not fear for our lives.

Bernard Katz was born and brought up in Leipzig, so his native language was German, though he was never a German citizen. Bert Sakmann relates that when BK first spoke to him in German (after his arrival in Biophysics in 1970), BK 'warned me that his German had a strong Anglo-Saxon accent'. This was a pun on the fact that BK spoke German with a Saxon accent that 'was indeed strong, and in Germany the Sächsische Akzent of people from Leipzig or Dresden is the source of many jokes'. The time when I recall BK laughing the most was when a young German, Florian Dreyer, was working in my lab. We visited BK in November 1977, to discuss results with tubocurarine. In the Haldane room at UCL, BK said 'It's a real pity that nobody here can understand jokes in Saxon dialect', but Florian did and they started swapping Saxon jokes in German, accompanied by peals of laughter.

BK's father, Max, was a fur merchant who had left Russia in 1904, and met his wife, Eugenie Rabinowitz, who was of Polish origin, in Germany. Until he was six, Katz was a citizen of Tsarist Russia, but then, because of the Russian Revolution, became stateless, and remained so until he was 30 when he became a naturalised British citizen.

In Leipzig, Katz was brought up in what he himself described as a 'completely "unorthodox" and liberal way', but nevertheless had his first experience of being an alien Jew in 1920 when, at the age of nine, he was refused entrance to the Schiller Real-Gymnasium (the head thought that it would be bad for their reputation to

Bernard Katz's school, the König Albert Gymnasium, Leipzig, in 1912 (left), and today

have the entrance exam topped by a foreigner –a Russian Jew), and consequently had a classical education at the König Albert Gymnasium.

There he chose to learn Latin and Greek rather than the more mathematical option (because, he said, it gave him more time to play chess in the cafés of Leipzig), though he acquired a good level of mathematics anyway. Despite his love of chess, and despite some unpleasant anti-Semitic experiences, he did well at school, and skipped a year. In his autobiographical essay he relates that one day, in the early 1920s, a fellow pupil had, in his absence 'called the boys together and informed them of a marvellous plan that his father had discussed with him at home. The plan was that the Jewish population of Leipzig should be invited to assemble in the underground fair hall, and after closing the doors should be killed off by filling the hall with poison gas' . . . 'This episode has never been erased from my mind, and it gives an indication of ideas that some people were harbouring in their heads for 20 years before they were able to put them into practice'. It is hard to appreciate what such an experience must have been like for a child of 11 or so.

Katz chose to study medicine, despite having no previous experience in the natural sciences, in part as a hedge against future financial problems. He started preclinical work at the University of Leipzig in 1929 (the classes started at 7 a.m.), where he was taught physics by no less than Peter Debye. He comments 'I suddenly realised the power and depth of scientific ideas and their continuous subjection to criticism and further trials by experiment. I felt almost revulsion against my previous preoccupation with what I now regarded as presumptuous philosophical speculations and with a genre of verbose literature that seemed to make a virtue of obscurities'. That reaction is

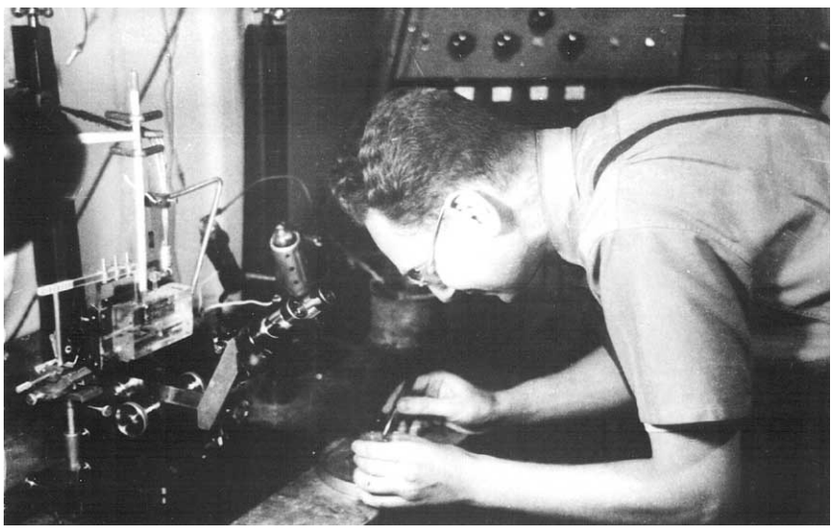
Martin Gildemeister (1876-1943)

A.V. Hill, c. 1935 (drawn by Edward Halliday in 1978, from a photograph)

certainly evident in BK's writing (and the same tendency can be seen in his disciple, Bert Sakmann, who, on being asked to speak to a distinguished philosophical society, told them that he actually preferred the motto of the Royal Society, *Nullius in Verba*, to philosophical speculation). His preclinical exams, taken in 1931, were entirely *viva voce*, the anatomy examination being conducted by Hans Held (of 'calyx of Held' fame), and the physiology exam by Martin Gildemeister.

After his preclinical exams, Katz combined his undergraduate work with part-time physiological research, under the supervision of Martin Gildemeister (1876-1943) who was interested in mathematical approaches to physiological phenomena. Working in the lab also had the advantage of keeping him away from the increasingly open anti-Semitic views of some of his fellow students. His work was on muscle stretch and impedance, and although he described the work as a 'prenatal effort', it resulted in two papers in *Pflügers Archiv*, which secured his MD degree and also led to his being awarded the Siegfried Garten prize. This was in 1933, the year Hitler came to power, and Gildemeister was forced to announce publicly that the prize could not be given to a 'non-Aryan' student, though he later gave Katz the prize money in private.

At some risk, Katz decided to complete his medical degree (1934) in Leipzig. During 1934 he had read A.V. Hill's Thomas Huxley lecture (given in Birmingham on 16 November, 1933), and had realised that the work he had been doing had some slight relation to work being done in Hill's lab at UCL. He had also read the correspondence between A.V. Hill and Johannes Stark, who had been an eminent physicist, but by this time was no more than a Nazi scientific Gauleiter. When Stark tried to defend the Nazi regime against Hill's criticism of their dismissal of Jewish scientists, Hill ended the correspondence by noting that gifts of money had been received in response to his appeal for assistance to help colleagues who had been driven out of Germany, but he was uncertain whether these donations were the result of his own eloquence, or rather should be attributed to Professor Stark's arguments, and he felt sure that some thanks were due to Professor Stark on this account. Katz quotes Hill as saying 'Laughter is the best detergent of nonsense' and goes on to say that these things 'gave me the first glimpse of A.V. Hill's personality, and I found it so attractive that I made every effort to go and work with him as soon as I could'. After working briefly in a Leipzig Hospital, at the beginning of February 1935, Bernard Katz packed his bags, took a third class train ticket to Holland, and then the Flushing-Harwich ferry. He was 23 and had only what he carried, a temporary British visa, his League of Nations stateless-persons pass, a letter of recommendation from



Working on squid axon, with Hodgkin, Plymouth Marine Lab, 1948 (Photo by Silvio Weidmann)

Martin Gildemeister and £4 in his pocket.

The next day, Katz climbed the stairs at University College London and met A.V. Hill for the first time. Hill was a remarkable man, not only a great scientist (he had received the Nobel prize, with Otto Meyerhof, in 1922), but also a statesman who took a large role in helping refugees in the pre-war period (see Katz's Biographical Memoir of Hill, 1978). It is very clear that Hill lived up to Katz's highest expectations. In his autobiographical essay Katz says 'It was an outstanding piece of good luck to have been taken on as an apprentice to A.V. Hill; it was the decisive influence on my life and career . . . He was the person from whom I have learned more than anyone else, about science and about human conduct. . . A.V. Hill was the most naturally upright man I have ever known. . . To be associated with a man of his stature at a formative period of one's life is indeed a great gift of fortune'. He described these first years in Hill's lab, between 1935 and 1939, as 'the most inspiring period of my life'.

Katz set to work at UCL on both nerve and muscle. Within a year his first paper with Hill appeared in *Proceedings of the Royal Society* (Hill *et al.* 1936). The full text of this, and of his many other papers in Royal Society journals are available on the JSTOR web site, though sadly his major papers in *The Journal of Physiology* are not yet so easy to obtain. Max Bennett of Sydney University has written a nice summary of Katz's scientific work (http://www.ibro.org/secondary/worldnews/index.asp?m=v&n=1005).

Shortly after getting his PhD at UCL, and a month before the start of the Second World War, he left Britain for Australia, where he worked with John Eccles and Stephen Kuffler. The work of Katz, Kuffler and Eccles in Sydney in 1940 and 1941 was, as Bennett points out, 'the beginning of a new era in synaptic physiology after the one begun 50 years earlier by Langley and Sherrington'. Use of more sophisticated electrical techniques allowed them to show, using an analysis provided by A. V. Hill, that transmitter action is very brief, and that most of the decay of the endplate potential occurs in the absence of transmitter. This became one of the basic beliefs about fast synaptic transmission for decades to come; it is undoubtedly true at the neuromuscular junction and at many (probably not all) central synapses.

Katz remained in Australia from 1939 to 1945, and in 1941 became a naturalised British citizen, so obtaining his first real passport. Soon after, he enlisted with the Royal Australian Air Force, and served as a radar officer on Goodenough Island, New Guinea, in the Pacific war against Japan.[1] 'The commanding officer of 305 Radar Station from October 1942 to March 1943 was Pilot Officer Bernard Katz' (http://rspas.anu.edu.au/papers/sources.html). John Eccles comments, in a letter sent at the time of BK's retirement, that 'In his nine months on Goodenough Island, behind the Japanese lines his station was never off the air'.

Later he met Marguerite Penly, known as Rita, who, incidentally, was not Jewish. They were married straight after the war. A month after the wedding he got a telegram from A.V. Hill inviting him to return to UCL as Henry Head Fellow of the Royal Society and assistant director of research in biophysics.

Katz returned to UCL in 1946, and

Pilot Officer Bernard Katz on the beach where a landing was made to reach Mwananoia (on north shore of Goodenough Island)

[1] Goodenough Island, Allied codename: MICROCOSM, formerly MORATA, one of the D'Entrecasteaux Islands, 20 miles (32 km) across Ward Hunt Strait from the eastern tip of New Guinea, in the Solomon Sea, southwestern Pacific. A part of Papua New Guinea, it lies northwest of Fergusson Island across Moresby Strait. The forested volcanic island, measuring 20 by 15 miles, rises to more than 8,000 feet (2,400 m) in its central mountain range. The island was visited in 1873 by Captain John Moresby, who named it after Commodore James Graham Goodenough. Occupied by Japanese troops for several months in 1942, the island was captured by Allied forces, who built Vivigani airstrip (open to commercial service since 1963).

his early work included the discovery of the phenomenon of inward ('anomalous') rectification. He also started a collaboration with Alan Hodgkin that led to the discovery that the overshoot of the action potential results from an influx of sodium ions.

In 1952 Katz succeeded A.V. Hill as Professor of Biophysics at UCL, where he headed a department of outstanding distinction until 1978. In the same year he was elected a Fellow of the Royal Society

The 1950s and 1960s were a golden era of important discoveries. With Paul Fatt it was established that acetylcholine, acting on receptors at the endplate, opens 'aqueous pores' in the muscle membrane. This was one of the roots of the modern idea of 'ion channels', though that term did not come into common use until later. During the 1950s, spontaneous miniature synaptic currents were observed (with Paul Fatt) and the essential facts about quantal transmitter release were established. For pharmacologists, his suggestion of a mechanism for partial agonism (del Castillo & Katz, 1957) was seminal. So was the first rigorous demonstration, by his PhD student Donald Jenkinson, that tubocurarine was a competitive antagonist, in a study that applied to the neuromuscular junction the methods devised by BK's fellow refugee at UCL, Heinz Schild.

BK's perceptiveness in distinguishing the important from the unimportant was legendary. He realised the small and unpromising spontaneous blips recorded at the endplate (miniature endplate potentials) were not just recording artefacts, but a phenomenon that eventually gave rise to the discovery of quantal transmitter release. A similar feat came 20 years later when he noticed that the increase in the noisiness of the recorded signal when acetylcholine was present was not as boring as it looked, but contained interesting information. His work on noise analysis with Ricardo Miledi in the early 1970s provided us with the first, albeit indirect, information about how single ion channels behave, and that allowed many of the remaining gaps in our knowledge of synaptic transmission to be filled in. Bert Sakmann arrived at UCL as this work was going on and relates how there was much discussion about whether recording from a single channel might one day be achieved. This of course, is something that

Portrait done in 1997, by Jenny Hersson-Ringskog (then an undergraduate student in Physiology-Pharmacology). The original hangs in the Starling room at UCL

The Bernard Katz building at UCL

The Orden Pour le mérite für Wissenschaften und Künste, awarded in 1982

Sakmann, with Erwin Neher, achieved not much later, in 1976, work that also got a Nobel Prize in 1991.

At UCL all the important features of synaptic transmission were established, and subsequently many of these principles have been found to be true in the brain too. The influence of his work is inestimable, not only in physiology, but also in pharmacology, in which he laid down some of the most important fundamental principles. He was justly rewarded by, among many other honours, the Nobel Prize in 1970, jointly with Ulf von Euler (of Sweden) and Julius Axelrod (of the United States), 'for their discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release and inactivation'.

Katz's retirement in 1978 certainly did not mean the end of his influence. He continued to referee papers (with an astonishing speed – often within a day or two), and he took a direct and lively interest in new developments for many more years. In the 1980s I remember him coming, almost running down the stairs, asking to see David Ogden (at that time a post doc in my lab), because he'd seen an abstract that David had submitted for a Physiological Society meeting and wanted to discuss it. During that time, too, I spent two hard weeks working on the mathematics in a paper about sodium channel inactivation because BK had asked about some details, and somehow if BK asked, it was inconceivable to say that one was busy. I personally owe him a great debt because his penetrating questions about the meaning of a 1977 paper that he read, before it was submitted to *Proceedings of the Royal Society*, led to a whole new field of work for me.

At UCL, Katz is remembered by the beautiful portrait drawn by an undergraduate student, by the creation of the Bernard Katz Chair of Biophysics (at present held by

BronzeTafel at the University of Leipzig

Jonathan Ashmore), and by the naming of a building in his honour.

Bernard Katz's work has been recognised in his birthplace in many ways, despite his never having been a German citizen. He was awarded the 'Orden Pour le mérite für Wissenschaften und Künste' (similar to the British Order of Merit) in 1982. This prestigious award was originally a military honour, but its military function ended in 1918, and the civilian version, founded by Frederick IV of Prussia in 1842 with the advice of Alexander von Humboldt, was reinstated in 1922. The charter of the award says 'The number of knights of this peace class is confined to 30 Germans; there may also be 30 foreign knights' (http://www.orden-pourlemerite.de/).

In 1990 Katz was given an honorary doctorate by his *alma mater*, the University of Leipzig, and in 2000 a bronze tablet was unveiled in the University grounds, by the Oberbürgermeister of Leipzig, the Dean of the Faculty of Medicine and the chairman of the Albertiner Bund ('old boys') of the König Albert Gymnasium. The existence of this memorial, and the wording on the plaque, was dependent on the efforts of, among others, Frederick Rose (now in Toronto), one of the few surviving 'Albertiner'. The inscription states (in translation) 'In honour of Sir Bernard Katz', followed by a brief CV which includes the words '1935 Emigration to England, because of repression on the grounds of his Jewish origin'.

BK did not himself supervise many PhD students (Paul Fatt, John Nicholls, William Burke, Bob Martin, Donald Jenkinson and Stuart Bevan), all of whom went on to do eminent work. But his department became a Mecca for postdoctoral students from all over the world. His influence on the training of a large number of the world's greatest scientists was huge.

BK's seriousness could sometimes make him appear forbidding, and there are many stories about experiences, sometimes quite traumatic, of presenting to him the first draft of a paper. Equally there are many stories of his jokes and light-hearted asides that punctured the pomposity of boring committee meetings. His lack of pomposity is nicely illustrated by an occasion in 1974 when a young PhD student was giving his first demonstration at a Physiological Society meeting. The demonstration involved voltage-clamp of muscle fibres, and his supervisor had properly suggested that when a visitor came in to see the demonstration, he should be asked if he was familiar with the methods before launching into an explanation. A middle aged man came in and 'I went through the motions and asked him if he was familiar with the method, to which he replied "..a little...". I then explained my demonstration, to which he listened patiently'. It was only later that the student discovered that his visitor had been BK, who had spared the student's blushes by not revealing his identity. It was the universal experience of his colleagues that he was a person with enormous enthusiasm, always willing to discuss with the most junior of them the details of their work and to offer advice. There can be few in the field of synaptic transmission and ion channels who have not benefited from his wisdom.

Although Katz spoke little English when he first arrived at UCL, his writing style was exemplary, and he was able and willing to correct the execrable style adopted by some native speakers of English. His prose was simple, straightforward and unpretentious, yet very precise, something that he attributed to his teachers at the König Albert Gymnasium. He would not use a long word when a short one would do, When it was proposed at the 1954 Mill Hill meeting of the Physiological Society that the terms 'sympathetic' and 'parasympathetic' should be replaced by 'orthosympathetic' and 'parasympathetic', his reaction to this quite unnecessary lengthening was to suggest 'sympathetic' and 'unsympathetic '(Bynum, 1976). His writing was totally free of the hyperbole that litters so many papers now, and also free of 'guest authors'. Those scientific bureaucrats who wish to force everyone to work in enormous groups should note that his papers rarely have more than two authors.

Bernard Katz had an uncanny knack for picking the important part of a problem, and to leave the rest of us dotting 'i's and crossing 't's. Every new entrant into the field should read his work from beginning to end.

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Acknowledgements

The historical facts in this article are largely culled from Bernard Katz's autobiographical essay, published in 1998. I have also had generous help from his sons, Jonathan and David, and many of his colleagues and coworkers.

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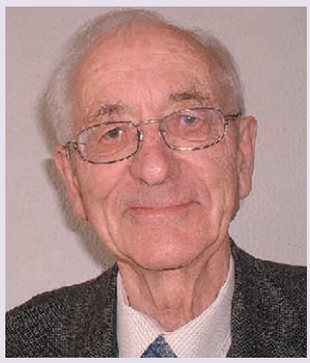
E. Geoffrey Walsh

1922 - 2003



Geoffrey Walsh was born in Cheltenham on 25 November, 1922. After education at Cheltenham Grammar School (1932-1940) he won a Scholarship to Exeter College, Oxford University to study medicine. He graduated BA with 1st class Honours in Animal Physiology in 1943, winning several undergraduate prizes.

Geoff began his research career in neurophysiology in 1944, still at Oxford, and published a Physiological Society communication with David Whitteridge that year. He then spent two years as a Rockefeller student at Harvard University, gaining an MD. Returning to Oxford, he graduated MA, BSc and BM BCh in 1947, and pursuing further clinical training gained the DTM & H at Liverpool University in 1948, worked for a while as a ship's surgeon, and qualified MRCP (London) in 1950. The next year he joined David Whitteridge, who had moved to the Chair of Physiology in the University of Edinburgh, as a Lecturer in the Department of Physiology.

His research was focused on the challenges of investigating neuromuscular control in humans, with a particular interest in the effects of vestibular dysfunction, and thus in the neurophysiological basis of balance, and of tremor. His research aims were generally directed towards understanding clinical neurological disorders, and to this end he was a part-time electroencephalographer in the Royal Infirmary of Edinburgh (1951-54), then an Honorary Consultant for the South East Scotland Regional Hospital Board (1957-63), later studying paraplegic patients, and in his last years he was Honorary Neurophysiological Specialist at the Royal Hospital for Sick Children, Edinburgh. This last appointment recognised his long interest in the motor control problems of spastic children, and led to studies on the shaken baby syndrome.

Meanwhile, his original research and scholastic contributions, ably described in Martin Lakie's tribute, and including his book *The physiology of the nervous system* (published first in 1957, and in a 2nd edition in 1964; translated into several languages) led to promotion to Senior Lecturer and finally Reader in 1967. His original contributions to human neurophysiology were recognised by Fellowship of the Royal Society of Edinburgh, in 1959, and his continuing interest in clinical problems by the award of Fellowships of the Royal Colleges of Physicians of both London (1967) and Edinburgh (1968). For example, in 1963-64, while a WHO visiting Professor at the Baroda Medical College in India, he advised the Tuberculosis Chemotherapy Centre in Madras on testing to identify vestibular damage from anti-tubercular drugs.

All the while Geoff was an active and loyal member of the Physiological Society, very frequently giving oral communications, and especially demonstrations at meetings of the Society. He was a member of the Editorial Board of *The Journal of Physiology* (1965-1972), a member of the Society's Committee (1983-86), and played a key role in the organisation of Society meetings in Edinburgh.

Geoff was bemused and dismayed by the academic leadership problems that beset the Edinburgh Medical School's Department of Physiology in the 1980s, and were still unresolved at his retirement in 1990, but, keeping close links, he enjoyed seeing the Department subsequently recover and flourish in the next few years. Geoff's valued contributions to teaching undergraduates, and the fact that he was continually research active for nearly 60 years, as evidenced by his publications, led the University of Edinburgh Medical School exceptionally to repeatedly renew his post-retirement Honorary Fellowship, which he still held on his death on 26 March, 2003 at the age of 80 years.

Geoff was particularly pleased to be awarded an extra-mural Professorship by the University of Central England in 1998, and the title of his inaugural lecture makes plain the multiple facets of his interests in human neurophysiology, including his late-developing interest in the fine control of finger movements in musicians, alongside his own learning of how to play the flute and the saxophone: '*Movement control in normals, the disabled and musicians: muscles, medicine and Mozart*'.

Geoff's wife, Penny, a charming, strong and supportive companion, died in 2000, and they are survived by three of their four daughters, and grand-children.

John A Russell
University of Edinburgh

Martin Lakie adds:

I first met Geoff Walsh 30 years ago. I was then a callow undergraduate student of physiology at Edinburgh. At this time I first entered the rather gloomy basement which housed the Human Neurophysiology Lab, and the intriguingly named Special Senses Lab, which were presided over by Dr E.G. Walsh and his technician Mr G. Wright (no first name status in those days). The labs and his office were very often home to Geoff's Dalmatian dog, Tasha. Experimental classes for students were overseen by the two gentlemen. For these

teaching sessions, Geoff would often wear his off-white lab coat which resembled, and might well have been,

a nightshirt of the Victorian period. Centre stage was occupied by a huge parallelogram action see-saw by which recumbent subjects could be propelled through a distance of a couple of metres towards the ceiling or floor. This apparatus had been built in order to test the vestibular sensitivity to linear acceleration in the saggital plane (Walsh, 1964a). These experiments, and others involving rotational vestibular stimulation were naturally popular with students who competed to achieve the highest velocities. Some years earlier there had been another apparatus that measured vestibular sensitivity in the transverse direction. To reduce shear forces on the skin the supine subject (breathing through a mouthpiece and valve) was entirely immersed in a deep coffin shaped tank of water suspended from the ceiling. In action, the water would slosh about and to minimise this disturbance it was rendered more viscous by the judicious admixture of wallpaper paste and sawdust. The subjects indicated that they had detected the stimulus by tapping with a hammer on the floor of the tank. Their reaction to the procedure is not reported (Walsh, 1961)

I remember at the time being impressed equally by the ingenious nature of the experiments and by the discovery that most of the apparatus had been cleverly constructed from a combination of vehicle, aircraft and marine scrap. There was, as I later discovered, an even deeper basement packed with gleanings from scrap-yards and surplus stores. Geoff's main early interests had been the sensory nervous system and he had an impressive number of publications on this work under his belt, and his erudite, entertaining and eclectic book (Walsh, 1964b) enjoyed a wide readership.

Working with Horace Barlow he had published two papers in 1947 on electrical and magnetic stimulation of the visual cortex (Barlow et al. 1947a, b). Half a century later Magstim experiments are now much in vogue. There was an early paper in *Nature* with Heinz Wolff (Walsh & Wolff, 1951) on the design of a novel beam splitting spectrophotometer. There were many papers on various aspects of vestibular sensation in animals and man. From this basis, his attention had broadened to encompass standing and balancing mechanisms, postural stability and instability and in particular, tremor.

I subsequently came to know Geoff well as I did a PhD under his supervision and worked with him as a postdoc for a number of years and we kept in touch thereafter. His industry, intelligence and enthusiasm were formidable and a little frightening at first. Fortunately, these characteristics were offset by a delightful sense of humour which was without doubt the driest that I have ever encountered. Although possessed of a dry sense of humour there was nothing arid about the man who had the most genuine curiosity about, and interest in, all aspects of life. He was in the true sense of the word a polymath. He once declared that it was his ambition to understand all scientific subjects to at least first year undergraduate degree level. As well as working hard in his spare time to achieve this ambition he also painted and played the flute. He was to some extent an iconoclast who cared little for uninformed opinion. It is hard perhaps to remember a time before the ubiquitous Walkman clamped over the ears became a commonplace. Many years ago I watched Geoff waiting in a busy public area of the Western General Hospital in Edinburgh as we whiled away the time before starting an experiment. He had over his ears a large pair of bright red earphones. Between the earphones was a centrally mounted radio receiver and a short vertical whip antenna sprouted from his head. The strains of Radio 3 were just audible. He gave every appearance of being oblivious to the interest that he was creating.

Although he was a scholar who loved to read and to write it is perhaps for his experimental work that he will be best remembered. He was an enthusiastic radio amateur and a very skilled builder of electronic apparatus, often of a high degree of complexity. The seamless transition from valves to transistors to integrated circuits and latterly to computers cannot have been easy to make. His electronic design ability was remarkable and he built a great number of novel circuits to carry out often complex analogue processes. While the design was invariably excellent, the standard of construction was often less perfect. Experiments would sometimes be punctuated by flashes, bangs and blue smoke as wires made accidental contact. On one memorable occasion a Physiological Society demonstration very nearly came to grief when widespread short-circuiting was found to have occurred because several of the rubber bands holding the circuit boards in place had perished. Such a technical malfunction would invariably trigger a reaction resembling that of a parent exasperated by a non-cooperating child. There would be an initial astonishment at the unexpected event, followed by a period of tutting and mild irritation as repairs were effected. This was characteristic; although an individual of very strongly held beliefs and principles he never publicly expressed more than a puzzlement and irritation at life's tribulations.

He was interested in travel and transport. Well known in Edinburgh was the steam car that he had designed and built although when I first knew him he generally travelled by motor-bike. There was a spare crash helmet and he would sometimes offer the unwary or naïve a lift on the pillion seat. With a group of researchers he measured head oscillations of volunteer railway passengers in a train consisting of

different models of carriage (Walsh, 1966). This train was specially run for the purposes of measurement on the East Coast line between Edinburgh and Newcastle. (He was particularly fond of the account of this work that appeared in *The Times* under the neat caption 'Heads roll on the 09.45'). He investigated in person the motion sickness caused by the effect of swaying gait of camels.

It is perhaps difficult to say what his main scientific interest was, but I would judge that his research always centred on recording and measurement, usually employing some highly original technique and self-constructed apparatus. If Geoff's research programme was perhaps less focussed and more curiosity-lead than would be generally approved of nowadays he nevertheless pursued important and complicated problems. Working sometimes on his own, but more commonly with a small number of colleagues, he made and is remembered for fundamental discoveries in four important areas.

First (Marshall & Walsh, 1956), there was his suggestion very nearly 50 years ago that physiological tremor represents in the main filtered noise which is generated by random motor unit activity. To this might be added the subsequent demonstration that it is the resonant properties of the limbs that imparts a colouration to the noise and gives it the appearance of a tuned oscillation. He was dismissive of 'tremor generators'.

Second (Walsh, 1969), he was one of the first to investigate the entrainment of pathological tremors using torque motors to 'drive' a limb. This ingenious approach can, in principle, distinguish between an oscillator which is autonomous and one which results from a process of self-re-excitation by a feedback mechanism. However, the resulting analysis is fraught with difficulties.

Third (Walsh, 1970), he was the first person to employ positive velocity feedback (negative damping) in order to make the human musculoskeletal system unstable and resonant. This technique has been recently used to study the operation of the CNS controller.

Finally (Lakie et al. 1984), following some pioneering work on the measurement of human muscle tone, he was able to demonstrate that human muscles behaved thixotropically, that is they had a stiffness which depended not just on the size of a movement but also on their history of movement. The implications that thixotropy has for the control of movement and the cause of the phenomenon are subjects which are currently receiving widespread attention.

Geoff maintained an active interest in research beyond retirement. He wrote his second book and finished a draft of a third. He had a laboratory built in his garden and he vigorously pursued the study of skilled finger movements in musicians and others. His findings were published on a regular basis right up to the time of his death. The possessor of an excellent memory, he was a fascinating source of recondite information on many aspects of neurophysiolog to the end of his life.

He was a colourful inhabitant of an earlier more colourful world. A world where the scope of scientific investigation was usually limited by the apparatus that could be constructed and the skill and intelligence of the investigator rather than by the size of the research grant that could be obtained. A world where intended learning outcomes, research assessment exercises, cost centres and teaching quality audit did not exist, yet good research was done and students were taught well. He once told me that he loved his job because he was paid for doing what he enjoyed most. That made him an amateur in the best sense of the word. Neurophysiology has lost one of its pioneers and the world is a greyer place for his death.

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Special senses teaching in Edinburgh

Andrew Packard reminisces on some of Geoffrey Walsh's ingenious additions to the Physiology Department's basement

My last 'phone call with Geoff Walsh in early March was about a version of the 'Asher Box' (Asher, 1950) (Fig. 1) I had built for students at Stanford University's Hopkins Marine Station. This box illustrates the simultaneous contrast illusion and opponent processing that takes place at the level of the retina.

Geoffrey, with his gift for resurrecting practical demonstrations from the literature, had had a copy of the original built by George Wright for small class teaching in the Special Senses lab at Edinburgh. The apparatus had a bulb in each of four chambers, those in the front chamber – the 'surround' of the visual stimuli – being operated by separate switches. I thought he would appreciate my cut-price version made

out of a shoe box with only a single, external, source of illumination. Apart from its ease of construction, the subtleties of centre-surround phenomena can be better demonstrated by dispensing with fixed light sources. Tracing paper in the cut out lid diffuses light from a lamp at the viewing end and students can see for themselves the effect of screening one, and not the other, of the front chambers, while leaving the rear ones, providing the 'centre', unchanged.

In my experience, Asher's psychophysical demonstration of the simultaneous contrast illusion is more effective than any of the better-known ones appearing in textbooks on vision.

Over the years, EGW and Hugh Begbie had added several ingenious pieces of apparatus to the special senses lab in the Physiology Department basement. At the bottom of the stairwell stood a huge swinging bed – a left-over from the period when EGW had a project on motion perception with British Rail. (They had lent him a train for a week operating out of Waverley station). On the bed would be a blindfolded student with a second in attendance recording sensations.

When I joined them in 1969, I was particularly intrigued by the things for vision - Begbie's speciality. There was a large bright (? xenon) lamp with filter in the far blue to see one's pulse and the trails of circulating rouleaux, while fixating a cross in the middle of the screen. When the blue

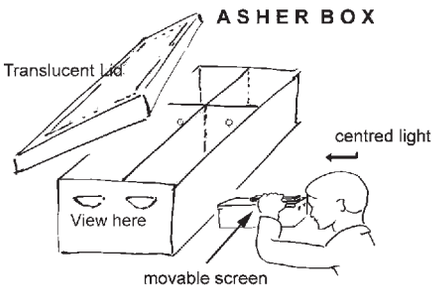

Figure 1. The Asher Box

The 'Asher Box' (Fig. 1), for demonstrating centre/surround properties of visual units, is made of two cardboard shoe boxes, with grey (or white) interiors, one for viewing and the other cannibalised to make internal partitions.

The viewing box is divided longways down the middle by one partition, and crossways by a second three-fifths from the viewing end to make four rectangular chambers. Two circular holes (c. 6 mm diameter) are punched in the cross partition with a leather punch or cork borer about two thirds up from the floor of the box on either side of the middle partition. [Find cork borer sets hidden away in old lab cupboards]. The flat part of the lid of the shoebox is cut out and replaced by tracing paper to act as a diffuser of overhead light. Spectacle-shaped apertures are cut in the end wall of the box for looking into the larger (front) chambers. The viewer sees one hole through into the rear chamber with the left eye, the other hole with the right eye.

In Asher's original design [as used in Edinburgh], the chambers were illuminated by four lamps: the two rear chambers by a 'pea-lamp' from a torch battery, the two front chambers by brighter lamps each with its own switch. In my version, illumination is from an overhead light, the relative positions of lighting and box being so adjusted that left and right sides are lit equally and the front chambers are brighter than the rear ones. The two holes in the cross partition should then appear of equal grey level. In the main experiment, illumination of the two rear chambers remains equal and unchanged.

The version created for teaching in Edinburgh had a stereoscope in the place of the peepholes for the two eyes, and one hole in the cross partition was higher than the other, but I find stereospecs are not necessary.

Uniformity of surfaces in the apparatus is unimportant; contrast is all-important. (A miniaturized photographic greyscale can be placed, for reference, on each of the 'surrounds').

Experiment 1 (the main experiment) demonstrates the centre/surround organisation of visual units. The viewer (participant observer) is asked a) to judge the relative grey levels of the two holes in the cross partitions, b) to comment on the effect of reducing the illumination of one of the front chambers with a screen – i.e. darkening the 'surround' on that side, c) to say whether his or her judgement changes when it is revealed that the absolute grey levels of the holes have not changed. By arranging that the two halves of the simultaneous contrast illusion were seen separately by the two eyes, Asher was able to argue that the units reponsible are at the level of the retina – a finding subsequently confirmed by neurophysiological experiments on monkeys.

Other experiments include demonstrations of red/green and green/red opponent processing (obtained by replacing the grey, or white, 'surrounds' by green and red partitions.

screen is viewed through a moving pinhole, the retinal capillary network supplying the fovea jumps sharply into view – complete with a gap at the centre corresponding to central fovea seen dimmer than the rest, where rods as well as capillaries are missing. (Of course the same effects can be achieved by looking at a blue sky on a bright day, but that is more difficult to arrange in Edinburgh).

Fortunately, some of these demonstrations survived the cuts and consequent abandonment of small class teaching in the Thatcher years. Suitably modified, they could be used to advantage in a darkened lecture theatre filled with 200 medical students where group reactions considerably enhance their success. We managed the Pulfrich Pendulum for binocular stereopsis suspending it from the pipes in the ceiling above the blackboards. From the back of a lecture theatre the pendulum appears to swing out across the heads in the front benches. We even simulated the Maurice-Ginsborg effect for perceiving one's own mini-saccades. Instead of an oscilloscope trace, the vertically-running spot of light is generated by a rotating slit in front of a stationary one mounted on the slide holder of a long-throw projector. The only trouble with these developments was that George was usually still perfecting the apparatus when the lecture was due to start! Other items can be kept to an inexpensive minimum: black-out paper for pinhole(s) and pieces of red and green acetate supplied to each student or shared between two. The colour filters also doubled up as neutral density filters to introduce the retinal delay (and retinal disparity) required for the Pulfrich Pendulum.

The large class also had other advantages. On one occasion, with the Ishihara charts faithfully reproduced as slides by Medical Photography, we picked up a rare female tritonope. And the colour filters allowed normals to see what it is like to be red-green colour blind, etc. With a class of 200 and everyone

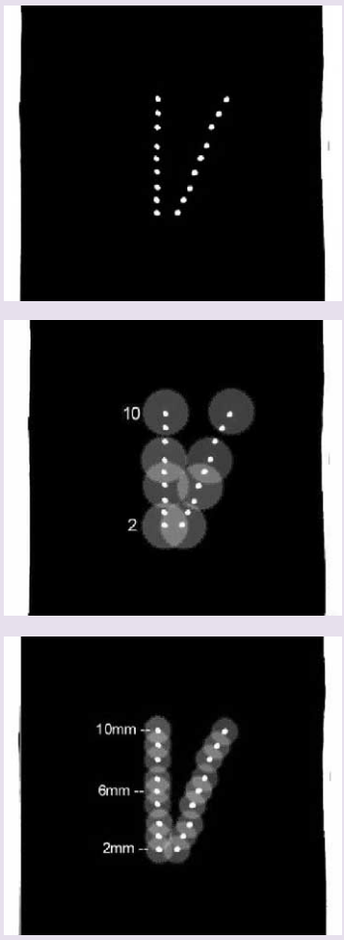

Figure 2. Top, Pupilometer (x1) consists of paired pinholes pricked through black paper progressively further apart: accuracy of pinhole diameters and shapes unimportant. It is held against one eye. Middle, 4 pairs of blur circles seen when contralateral eye is covered. Below, blur circles during consensual reflex, (contralateral eye uncovered).

able to see their own blur circles (Fig. 2) they could measure (and we could do instant statistics on) male and female pupil diameters during the consensual reflex.

As always with teaching, it acted as an incitement to research. One piece of apparatus not suitable for the large class was a pointing experiment – described in Walsh's book on the Nervous System as a 'projectionometer.. Author/unpublished' (Walsh, 1964, Fig. 9.19). It tests the accuracy of locating a brief spot of light imaged at intervals along a scaled board, while fixating a central light. Plotting the responses of a number of subjects I noticed that accuracy was worse on the left side of the board than on the right, irrespective of whether pointing is with the left or the right hand. Most responses fall short of the target, and the shortfall is greater in left visual field than in right – to do with hemispheric separation of the two fields, I suspect. As I enter our darkened living room, my eye movements cause the light of the digital clock on the radio to appear as a bright line interrupted at 50-cycles. When I look to the right, the line is longer, brighter and the regular interruptions more spaced than when I look to the left. I have no reason to believe that this strange difference is because the velocity of my 'look left' saccades is less than that of my 'look right' ones. So I conclude that the perceived difference in the saccades has the same origin as the perceptual 'contraction' of left visual field observed in the pointing experiment.

Has this directional difference on the perceived amplitude of one's horizontal shifts of gaze been noticed by others, I wonder?

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Emiline Lesly Jervis

1927-2002

Emiline Lesly Jervis was recruited to the Department of Physiology at Sheffield University by Professor David Smyth as a Research Assistant in 1955 to join his team investigating the mechanisms of intestinal transport of hexoses and amino

acids. Research on the intestinal absorption of amino acid enantiomorphs (the title of her thesis) led to her PhD in 1960 two years after becoming a Lecturer in Physiology. Three papers were published with David Smyth in *The Journal of Physiology* on the topic between 1959 and 60. She was elected a member of the Physiological Society in 1960 and became a Senior Lecturer in 1974. Lesly, who was diabetic, developed diabetic retinopathy and began to experience impaired vision. She struggled against the condition and was able to produce enough results for the basis of a paper co-authored with Dr Roy Levin that was published in *Nature* in 1966. Unfortunately, it became her last major publication as her eyesight continued to deteriorate and she became sighted in only one eye. It made for great difficulty for her experimental bench work and when the sight in this eye also began to deteriorate she was finally forced to give up experimental work. Despite her sight disadvantage she devoted herself to teaching physiology to dental students and administered their course for many years. Gradually her condition worsened, she became practically blind and only then did she decide to take early retirement on health grounds retiring from the Department in 1985. She died in hospital in Sheffield in 2002 aged 75.

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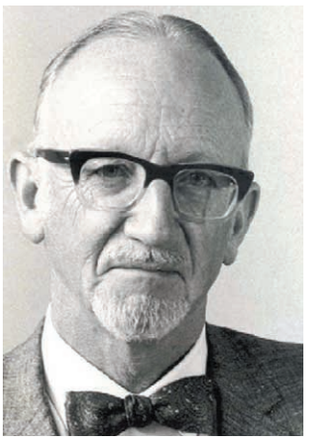
Archie McIntyre

1913 – 2002

Archie McIntyre died on the 20 July, 2002. The Foundation Professor of Physiology at Monash University, Melbourne, Archie can be considered to be one of the founders of modern neuroscience in Australia. This piece is based largely on a series of conversations I had with Archie about his life and work. The meeting took place in June 1994. The first part of the account is about his life.



At the end are included some more general views held by Archie, in summary form. Archie has read the transcripts of our meeting and was in essential agreement with what I had written.

Archibald Keverall McIntyre was born on 1 May, 1913 in Edinburgh, Scotland, the second of four children. His father, Bill, who was from Hobart, Tasmania, had studied engineering in Sydney and during his time there had met and married Margaret Edgeworth David, daughter of the Professor of Geology.

Edgeworth David was a distinguished scientist and scholar who came to Australia in 1882 as Assistant Geological Surveyor for New South Wales. He became Professor of Geology at the University of Sydney in 1891. In 1907, the *Nimrod* called at Sydney, with Lt Ernest Shackleton's Antarctic expedition. David accepted an invitation to join the expedition as geologist, bringing along Douglas Mawson, one of his Honours' students. During the summer of 1907/08, David led a party which climbed the active volcano Mt Erebus. In 1909, with two others, Douglas Mawson and an Englishman, Alistair Mackay, David reached the South Magnetic Pole, a round trip of about 1200 miles: this without food depots and without dogs to pull their two sleds.

During the birth of their first child, Peggy, Madge McIntyre developed puerperal fever from which she eventually recovered. This incident contributed to Bill's decision to abandon engineering and to study medicine.

With some financial help from his famous father-in-law he went to Edinburgh to study medicine. That was how Archie came to be born there. Bill graduated in medicine in 1915 and joined the British 80th Field Ambulance which saw service first on the western front then, until the end of the war, in Macedonia. Bill returned to Edinburgh in 1919 when Archie really got to know his father for the first time.

In 1920 the family returned to Launceston, Tasmania where Bill set up his practice and remained there for the rest of his life. Archie first went to school at the age of eight. His mother, a highly cultivated and intellectual person had already taught him his 3Rs and much more. Archie attributes his love of poetry to his mother. Archie's first years at school were not very happy ones because he already seemed to know most of what was being taught. It was not immediately recognised that he was acutely short-sighted and couldn't see the blackboard from the back of the classroom. Subsequently his parents decided that Archie should continue his education in Sydney and so he spent the last four years of secondary school at Barker College Hornsby. He matriculated in 1929. During this time he got to know better his famous grandparents as well as his aunt Molly whom he subsequently referred to as his second mother. At age 16, having won a university exhibition, Archie enrolled for a BSc at Sydney University, studying physics, chemistry, zoology and botany. This was Archie's first introduction to biology which in those days boys never did at school, and he became deeply fascinated by it. His interest in biology and encouragement from his father led Archie to transfer to medicine in his second year.

Although he found medical school

initially difficult, his organised approach to learning and his excellent memory meant he was soon at the top of his class. He was one of the select few to be chosen for 'prosector' in anatomy. Archie's first introduction to neuroscience came through one of the lecturers, Kanny, who also worked part-time at the Kanematsu Institute. After his third year, when Archie again passed with high distinctions he was the only student to do an Honours year, our equivalent of the Bachelor of Medical Science. He worked on blood gas analysis with Witridge-Davis. It was amusing to hear Archie's account of how he managed to take blood samples from himself 'using bits of string and sealing wax'.

Archie did his residency at Prince Alfred Hospital. During these later years he was befriended by Burkett the Professor of Anatomy. He also had good relations with Harold Dew, the Professor of Surgery. In the Department of Surgery Archie began working on the sense of balance by making recordings from the 8th nerve. Here Burkett with his excellent library was often able to help. Burkett also arranged for Archie to give some of his first lectures. It was during this time that he began to get to know better his future wife, Anne. They had met earlier, when Archie was staging a play at his aunt Molly's. They became engaged in 1939 and married in 1940.

Archie's interest in the sense of balance led him to study eye movements. He recorded eye movements with simple surface electrodes and a string galvanometer and discovered to his astonishment that the eyes moved in the opposite direction to the head. This led to his first paper in *The Journal of Physiology* (McIntyre, 1939).

His work in obstetrics at the Prince Alfred and subsequently at the Royal Children's Hospital left him with a deep interest in the birth process. He began developing methods of recording uterine contractions during labour. Subsequently he studied the responses of isolated strips of uterine smooth muscle to electrical stimulation and hormones added to the bathing solution.

At the outbreak of war Archie was persuaded to join the Air Force. Making use of his interest in the vestibular system, he developed a method of identifying air sickness-prone subjects. These were then eliminated from pilot training in the USA or Britain. He began to work on anti-blackout suits for pilots. He was assigned as medical officer to Frank Cotton who ran an experimental centrifuge in Sydney. Subsequently Archie was sent to the USA to visit centrifuge labs there and to Britain where he worked for a time with the Physiological Aviation Medicine Unit run by Bryan Matthews, which was based near Farnborough. There the work was on ejector seats. Notably, Archie participated in all of the experiments himself, some of which were quite dangerous, because he was of the view that you couldn't ask others to do what you were not prepared to do yourself.

Archie was demobilised in 1946 having reached the rank of squadron leader and, as he put it, having no squadron to lead. At this time he was approached by Pansy Wright, Professor of Physiology at Melbourne University, who offered him a lecturing post. However, Archie wanted to go overseas to one of the top laboratories to further his postgraduate training. He had briefly visited the Rockefeller Institute in New York at the end of the war and there met Herbert Gasser, the director and Dave Lloyd whose interests were in reflexes. Archie was awarded a Rockefeller Fellowship and during the years 1946-1948 worked at the Institute. The rather small stipend made life in New York hard for the family, but somehow they managed. Other well-known neuroscientists working at the Institute at the time were Lorente de No, a student of Cajal and Birdsey Renshaw. Archie worked with Lloyd on the tendon jerk. This was one of the foremost laboratories in the world, equipped with the most modern valve operated electronics.

Towards the end of his time in New York Archie got a Nuffield Scholarship to work in Cambridge. (At about this time his mother was killed in a plane crash on her way back to Tasmania from a meeting of the National Council of Women in Brisbane). In Cambridge Archie borrowed a bicycle from Alan Hodgkin to travel to the lab every day. Here he had to build his own equipment, a muscle stretching device for frog muscle. During his stay in Cambridge he got a lot of help from Bryan Matthews, the Head of Department.

While in Cambridge Archie received an offer from Jack Eccles to take up a senior lectureship in Jack's department in Dunedin, New Zealand. This vacancy arose from the departure of Vic McFarlane to the Chair of Physiology in Queensland. Eccles was probably particularly interested in Archie because he knew Archie had worked with Lloyd in areas of interest to him. At this time Eccles and Lloyd were locked in a debate about the latency of direct inhibition, a debate which Eccles eventually won.

Archie had first met Eccles while they were both still in Sydney. Jack was head of the Kanematsu Institute and Professor of Pathology. At this time Archie also met Bernard Katz and Stephen Kuffler both of whom became good friends. During his time in Cambridge Archie visited Bernard Katz at University College and obtained all of the necessary technical details for making microelectrodes. He took this information with him to Dunedin where with help from Jack Coombs he built a set-up for recording from spinal neurones with microelectrodes. Initially Eccles was not interested but he soon realised the importance of this technique. He began using Archie's equipment for

experiments that would ultimately bring him the Nobel Prize. Archie was obliged to go and work on something else.

During the early years in Dunedin Eccles and McIntyre briefly worked together. This was work on chromatolysis in motoneurones and on disuse. Archie did most of the dissections because he was so much better at it, having been trained by Lloyd. In writing up the experiments it seemed that Eccles always wanted to speculate further than the evidence allowed and often the speculation was declared as a firm conclusion.

In 1951 Eccles took up the chair at the ANU in Canberra and Archie became Acting Head in Dunedin, then Head in 1952. Archie remained at this post for the next nine years, perhaps some of the happiest years of his career. Many students passed through Archie's department some of whom later became well-known in their own right, people like W.I. McDonald, Peter Gage, Julian Jack, Richard Mark, Ainsley Iggo, John Ludbrook, John Hubbard and Austin Doyle. Archie attracted a zoologist, Geoff Satchell, to the department and John Veale who had double degrees in Physics and Medicine joined him from Auckland. Many years later, it was Geoff Satchell who introduced me to Archie.

In 1953 Archie gave a paper in Montreal on the disuse work with Eccles and he used that occasion to spend a couple of months back in Dave Lloyd's lab. Lloyd was working with Cuy Hunt at this time. Hunt and McIntyre became close friends. Archie was also deeply impressed by Herbert Gasser, the director of the Rockefeller. Apparently Gasser used to wander into the laboratory rather casually and in the ensuing conversation was known to often make, in passing, rather pertinent remarks about some problem or other. So it was with Archie - Gasser mentioned that little was known of the properties of the cutaneous sense organs supplied by the peripheral nerves which he, Gasser, had studied. This comment eventually led to the three landmark papers on sensory receptors by Hunt and McIntyre (1960a, 1960b, 1960c).

During 1959-1960 Archie took study leave, six months at University College, London, then a second six months in Salt Lake City, Utah. In Utah, Archie and Cuy carried out the experiments that led to those three papers. There he also met Ed Perl and Carlos Eyzaguirre.

Late in 1961 Archie was invited to apply for the Chair at Monash University, and after some hesitation he accepted. His recollection of the early days at Monash were that everything seemed to change so rapidly. He would plan buildings for a set number of students, then that number would be doubled. Archie was concerned that he had to set up a whole department from scratch. He put much importance on the selection of staff and soon it was a vigorous, thriving department, establishing its reputation locally and overseas. Archie believed that the best approach to the teaching of neuroscience was an integrated one. However, many of his early attempts in this direction were frustrated by the lack of cooperation from other departments.

In 1963 Archie was elected to the Australian Academy of Science. He became a Member of Council of the Academy from 1968-1974 and in 1970 was elected Secretary, Biological Sciences. During this time he was involved in many activities relating to Physiology and Neuroscience. He was President of the Australian and New Zealand Association for the Advancement of Science (ANZAAS), on Australian Research Grants Committee (ARGC) and National Health and Medical Research Council of Australia committees, a member of the Programme Committee of International Union of Physiological Sciences (IUPS) and Chairman of the National Committee for Physiological Sciences. Archie retired in 1978. In 1981-1983 he was the inaugural President of the Australian Physiological and Pharmacological Society (APPS).

Archie and Anne retired to Launceston, Tasmania, where Archie had a brother and sister as well as nieces and nephews. Anne designed and supervised the construction of their home, Montacute, perched on the crest of a ridge, overlooking the Tamar Valley on the outskirts of Launceston. At this time Archie became interested in wine making. Here his thorough training in chemistry came to the fore. About 50 vines were planted and soon Archie and Anne were self-sufficient in wine supplies. I remember, from time to time, sending Archie various pieces of glassware and other laboratory items to help equip his blossoming oenological analysis laboratory. Even today empty bottles of various Montacute vintages adorn the shelves of my laboratory.

In retirement Archie remained in touch with some of the areas of his interests, which included comparative neuroscience. In the period 1982-1990 Archie came out of retirement at regular intervals to carry out experiments with myself and friends. With John Rawson we showed for the first time that tendon organ afferents projected to the cerebral cortex. In a memorable series of experiments in which Ainsley Iggo and Ed Gregory participated, we began to explore the electric sense in the platypus. These experiments often went on all night. I remember the recording sessions would be interrupted, from time to time, by deep philosophical discussions and there were occasions when Archie would burst forth with a stanza of one of his favourite poems. We all got a lot of pleasure out of these collaborative efforts and for me it was a time when my friendship with Archie grew ever closer.

During the subsequent years Archie's health deteriorated and he and Anne

eventually found it necessary to leave Montacute to come and live in a retirement village close to the centre of Launceston. After a brief illness, Archie died in hospital on the morning of Saturday 20 July, 2002. He was 89 years old.

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Acknowledgements
I would like to thank members of Archie's family, particularly his wife Anne, for talking with me about Archie's life and work. I also thank Archie's sister, Anne, for her comments on the manuscript and for providing some of the historical details.

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(This obituary was first published in *Clinical and Experimental Pharmacology and Physiology* (2003) **30**, 303-306.)

Some of Archie's personal views

Concerning the research activities by members of staff of a department

Archie believed that while not everyone has a natural aptitude for research, everyone should be encouraged to do something. Those who are unable to initiate projects by themselves should be encouraged to join other existing active groups. If someone only teaches, and teaches the same thing year after year, they become stale and their views out-of-date as the field moves on. It is important to be personally involved in some aspect of the work which one teaches, to be doing something new, something different. It is also important in the lectures to give the students a historical perspective of the subject. In doing so it will remind them of the continually evolving nature of knowledge and hopefully instil in them a sense of humility, an awareness that the present state of knowledge is only one step along a never-ending road. In presenting this kind of view it is especially helpful to draw from personal experience, how one's own contribution came about and how it was incorporated into the body of knowledge. For most of his life, Archie was interested in the workings of the brain. Despite much progress, so very little is known about it, even today. It is in this kind of situation where a scientists' sense of humility is important.

Looking back on his career, what are some of his fondest memories?

First and foremost there are the students. He learned so much from them. And at all levels. Sometimes at the end of a lecture an undergraduate student would ask what at first sight seemed a silly question. On reflection, it often turned out that the answer was not at all obvious. There were even occasions where it could lead to a new line of inquiry in research. Most of Archie's students have kept in touch over the years and it was a constant source of pleasure to him to see them succeed in their work.

Pure versus applied research

The discussions over this question seem to have heated up in recent years. In the early days, whether something had a useful, practical outcome was a consideration, but not a major one. If research is not driven by the pressures of a useful outcome, the work often seems to be more objective. And who is to say what knowledge is going to be useful, and what isn't? Research should also be part of someone's intellectual training, to try to find out something new, if they can. Here the intellectual achievement should be rewarded, not the practical outcome. Research and research-related activities seem to be good for the morale of a university department. Another trend in recent years is to tailor research programmes to the duration of the period of external funding. The risk is that people will tend to pursue the funds rather than the knowledge.

The future of neuroscience

There is obviously an enormous contribution now being made by molecular biology. But remember, many people came into molecular biology trained as biochemists, microbiologists or immunologists. There is therefore the risk of losing the broader view. It is important to consider the organism as a whole and to try to understand integrative aspects. For that it is necessary to have a good general knowledge of biology. Concerning our understanding of the brain, obviously some of the recent work, at the cellular level, on isolated brain tissue has had a major impact. Again it will be important to assemble the various parts into a meaningful whole. Perhaps computers will be able to help, as well as modern imaging techniques. Finally, construction of models of how the brain works are well and good. But they must be firmly based on experimental observations and they are only as good as the questions they raise, questions that can be tested by experiment. An all-embracing model that purports to explain everything, stifles enquiry and leaves us with a false sense of assurance about our understanding of the world around us.

Inaugural Lecture

Regarding the sad death of Sir Bernard Katz, I was browsing among some old papers in a second-hand book store in Glasgow a few years back and came across a print of Sir Bernard's Inaugural Lecture (Different Forms of Signalling employed by the Nervous System. An Inaugural Lecture delivered at University College London on 31 January, 1952. Published by H.K. Lewis & Co Ltd). I enjoyed reading this enormously and thought it might be of more emotional value to any of our Members who perhaps actually aattended the Lecture and had no record of it. I have therefore passed it to the Publications Office and it will be made available on the Society's web site (www.physoc.org)

Chris Hillier
Glasgow Caledonian University

David Horrobin

1939 – 2003

David Horrobin, who died of lymphoma on 1 April was a 'full-time' physiologist for only the early part of his career. Because of this, I suspect his name may be less well-known to Society members than to people in medicine or the pharmaceutical business. However, he remained an active member of the Society throughout his working life, a testament to his lifelong search for new ideas, particularly in the area of research into polyunsaturated fatty acids, and latterly into schizophrenia.

David was a true 'renaissance man'. He was, *inter alia*, scientist – and one who experimented on himself at that - teacher, author, journal founder and editor, publisher, research charity president, entrepreneur and CEO. More than enough for several lifetimes - and I have probably omitted several other roles. He was also someone who spoke his mind – frequently and eloquently – and rather enjoyed a good argument.

The bare facts of David's career are remarkable enough. He won a scholarship to Oxford to read Medicine and, following clinical and research training in London, became Professor of Medical Physiology in Nairobi at the age of 31. From there he moved to Newcastle as Reader in Physiology in 1972, and to Montreal as Professor of Medicine in 1975. In 1979 he left academia and began the second major phase of his career when he set up the Efamol Research Institute in Nova Scotia, which spawned the biotechnology company Scotia Pharmaceuticals in 1987. David ran Scotia until leaving the company after a boardroom struggle in 1997 to form Laxdale Ltd, which he ran until his death.

I got to know David well in the 70s during three years he spent in the Newcastle Physiology Department and subsequently when he persuaded me to found and edit the journal *Cell Calcium*. Characteristics of his that most stick in my mind are his intelligence, his unflagging enthusiasm for new ideas and his generosity. David was always trying to do something new, and was never content to stand still. He was also an excellent teacher and inspirer of others, always ready to spend time with people to get the point across.

David was also, needless to say, prolific. When he came to work in Newcastle he was already the author of a classic textbook for medical students, written during his time in Nairobi, and of several other books besides, including a noted guidebook to East Africa! He published a huge number of articles and several more books, culminating in his recent *book The Madness of Adam and Eve: Did Schizophrenia Shape Humanity?* (Bantam Press, 2001), which was short-listed for the Aventis Science Book Prize the following year.

Throughout his career David was always ready to argue his ideas in print, whether scientific or in what one might call the 'politics' of refereeing and funding. This outspokenness meant that some in the scientific and medical establishment viewed him as an irritant. But it is David's later career as a pharmaceutical scientist-entrepreneur that generated the most controversy, both in his lifetime and beyond it. Scotia promoted polyunsaturated fatty acids (PUFAs) and products containing them, notably evening primrose oil, as potential remedies for many conditions, and funded both basic and clinical research into their actions. Only a few of these potential uses have resulted in accepted treatments, which has led some commentators to view David's work at Scotia with a slightly jaundiced eye – somewhat harshly, I feel, given the enormous difficulties in bringing new medicines to fruition. Although Scotia is no longer trading, a search on Medline reveals that research into gamma-linolenic acid continues – with nearly 100 papers published in each of the last three years – and the importance of PUFAs in physiology and medicine cannot be disputed. As a tireless promoter of research into PUFAs, David Horrobin deserves to take some of the credit for this.

Numerous obituaries of David Horrobin appeared in the national and specialist press. Several are worth reading, notably those in the *Times*, *The Scotsman*, and *The Lancet*, but the one that has attracted the most attention was a bizarre, negative, and deeply ill-judged one which appeared in the *British Medical Journal,* and which caused considerable hurt to David's family. What the author of this hatchet-job had against David is hard to fathom, but she unwittingly ended up providing him with a rather special memorial. Within days of the obituary appearing, over 100 people – friends, family, former colleagues and other researchers, or just plain interested readers – had written in to the *BMJ* to reject her verdict on David and, in many cases, share their reminiscences of this exceptional person. This response exceeded in volume the correspondence produced by any other piece the *BMJ* has ever printed. The letters, which can be read on the *BMJ* website, make fascinating reading, and give a real sense of the man, his life and work, and above all his gift for inspiring others.

Maynard Case
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Mechanisms and Consequences of Proton Transport

Tetsuro Urushidani, John G. Forte, George Sachs
Kluwer Academic Publishers, US$112, 372 pp.
ISBN 1-4020-7059-4

Appropriately, I washed down my ranitidine with a strong black coffee to set me up to read this book. This volume is a typical synthesis of conference proceedings, with the inevitable diverse range in quality of contributions that this brings. Pasting presentation blots, real time imaging, immunohistochemistry, etc. directly into the authors texts results in an unfortunate number of barely clear or totally uninterpretable figures, with some outstandingly small reduced fonts (a few just visible if held very close in a good light). Nevertheless, the book provides an excellent snapshot of where gastric proton pump physiology, predominantly molecular and cellular, is, or at least was in August 2001. The Pharma sponsorship of this meeting by several leading Proton Pump Inhibitor (PPI) manufacturers is noted.

Unfortunately, this book delivers only in part on its title: 'mechanisms' are covered in fine detail, with a particularly sturdy first section on structure and function of H^+,K^+-ATPase, and with welcome contributions about colonic and renal family members, which comprise different heterodimers. This section also includes curiously placed chapters on duodenal bicarbonate secretion and the effects of ethanol on gastric cell volume and gap junctions. Further sections include a strong set of contributions on transgenic mouse models and proliferation, insights into parietal cell signal transduction, and studies of the parietal cell cytokeleton and membrane trafficking, important given the profound structural changes that occur in a stimulated parietal cell and accompanied by some impressive scanning EM imagery.

However, the second part of the title, the promised 'consequences of proton transport' failed to really materialise much, and this is where the interest really lies in practical (all right, clinical – I have to admit here to being a practising clinician) terms. The presented work fails to convince that, for other than the reductionist purist, the proton pump is deserving of such ongoing attention. PPIs are arguably the most clinically effective drugs in *any* current usage, and it is difficult to see that other upstream parietal cell signalling pathways could ever become more attractive therapeutic targets than the final common pathway, i.e. the proton pump itself.

Clinically, diseases of gastric acid secretion are almost always soluble by current therapy. A few patients may be less sensitive to PPIs and other drugs, and it would have been interesting to see a pharmacogenomic contribution in the structure:function section. However, it seems to me that the real future of this field lies more in the consequences of *inhibition* of proton pumps, either by drugs or by *H. pylori*- induced parietal cell atrophy, and the trophic effects of the secondary hypergastrinaemia which results. This will require less reductionist models for study, and more joined-up physiology, such as that facilitated by the gastrin transgenic models presented herein.

One final point; it was good to know the book was printed on Acid Free Paper.

John McLaughlin
University of Manchester

Review of Exercise Physiology: People and Ideas

Edited by Charles M Tipton Published for the American Physiological Society by Oxford University Press, New York, £69.50 (hardback), 510pp. ISBN-19-512527-4

This volume is part of the People and Ideas series of the American Physiological Society. As Charles Tipton, the Editor, makes clear, the acknowledgement of the existence of

Other books received

Those marked with an asterisk (*) are still available for review. Any reader wishing to receive the book and write a short review should contact lrimmer@physoc.org

*** Proteinase and Peptidase Inhibition.** Recent potential targets for drug development. Edited by H. John Smith and Claire Simons. Taylor & Francis, 412 pp. ISBN 0-415-27349-8

Signalers and Receivers. Mechanisms and evolution of arthropod communication. Michael D. Greenfield. Oxford University Press, 414 pp. ISBN 0-19-513452-4

An Holistic Guide to Anatomy & Physiology. Tina Parsons. Thomson Publishing Services, £15.99, 282 pp. ISBN 1-86152-976-7

exercise physiology as a sub-discipline of physiology in the American Physiological Society is a relatively recent development, although studies of the physiology of exercise *per se* in the modern sense are roughly 100 years old.

In his introduction Charlie Tipton mentions the fact that exercise elicits integrated physiological responses but the contributions almost completely ignore this aspect and deal with the development of current ideas concerning the operation of various systems of the body during exercise. The contributors, many of whom I know personally, are certainly what would now be regarded as elder statesmen of the field (with the sad exception of Carl Gisolfi who died after submitting his chapter). This places them in a good position to review the historical developments in their area, especially since almost all of these developments have occurred in the last 30 years - and the total literature does not extend much beyond 30 years earlier than that.

In reviewing this book I found myself asking a number of questions. Would I use the book in preparing lectures or giving seminars to senior and postgraduate students? Did the book give me insights into areas of physiology beyond that in which I work? Was I engrossed in the stories told? Were photographs of the participants and their laboratories illuminating? Most of my responses are positive and although sometimes some of the participants are a little self-serving in describing their own achievements within the history of the subject, there were no egregious errors that I could spot. I was a little disappointed that there was so little on biophysics of muscle contraction, especially since the classic monograph of Woledge, Curtin and Homsher is now 18 years old (Woledge et al, 1985). None of the contributions gave me as much intellectual pleasure as reading the same subjects covered at about the same degree of detail in Dorothy Needham's wonderful book, now 30-odd years old (Needham, 1971). However, as she says in the introduction to Machina Carnis, she spent years writing it. None of the authors of this one have had that luxury. Given the constraints on their time, they have done a rather good job although I think it is a great pity that the Editor did not persuade Dirk Pette or Gerta Vrboba to write on the mutability of muscle fibre types, and the whole question of protein metabolism in exercise, in which I am particularly interested, gets no mention whatsoever (though a couple of my own earlier papers are cited, I'm pleased to find).

There are some sloppy and some hilarious aspects to the book. My old mentor, Richard Edwards, is mentioned in the index but only one of the pages cited deals with him, the other dealing with some other Edwards. And, astonishingly, despite one of the scientists pictured in a snapshot of Whipp and Wasserman being a co-author of the chapter in which the photograph appears, the legend has their positions in the photograph transposed! Very Freudian!

So, all in all a book to dip into, one from which to pilfer anecdotes to introduce lectures and certainly one from which to extract many examples of the foolish persistence of brilliant scientists in following patently wrong directions (e.g. the venerable A V Hill's insistence that lactate was the cause and not the result of muscular contraction). Anything which helps persuade young physiologists that scientific life did not begin 10 years ago is a good thing.

Michael J. Rennie
University of Dundee

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Diseases of the lymphatics

N Browse, KG Burnand & PS Mortimer. London: Arnold, 2003. 336 pp, £145.00. ISBN 0 340 76203 9

All physiologists know about the importance of the lymphatics, at least in a rather theoretical sort of way. But even 106 years after Starling laid the foundation for our modern understanding of lymph formation, the lymphatics remain substantially a hidden system, perhaps not least because it's the red stuff that grabs our attention if we hurt ourselves or if it stops going round. Everyone knows who inferred the circulation of the blood and many could probably dredge up the name of the chap who proved the circuit by describing capillaries. But I doubt if even a handful of readers could name the people who first described the lacteals and peripheral lymphatics, or who first correctly suggested what lymphatics are for (I was certainly guilty as charged).

This exceptionally well-illustrated book is an excellent antidote to lymphatic vagueness. It is divided into two parts, the first dealing with general principles and the second with the management of clinical problems. In the first part there are highly informative historical and anatomical overviews, as well as a good description of the formation and propulsion of lymph. The surgical pathology of the lymphatics is well-described, though as a pathologist and erstwhile physiologist I was disappointed that the pathophysiology of the lymphatics – for example their role in immunosurveillance, lymphocyte circulation and particulate matter transport – was hardly covered. Other chapters deal with development of the lymphatics, the classification and diagnosis of lymphoedema and the general principles of medical and surgical treatment.

I'm sure that these latter chapters, as well as the whole of the second part of the book, will be a real eye-opener for many physiologists, putting flesh (as it were) on their theoretical understanding of the lymphatics. It's quite easy to write the Starling equation on a blackboard and declaim its importance to dazed groups of students for many years without ever really appreciating how anatomically devastating the effects of lymphatic dysfunction can be. You will be in no doubt after a look through this text.

Another point which came over strongly to me (and which may be salutary for those who feel that ever more detailed basic science is the key to solving humanity's ills) is that there are often times in human disease when even a highly detailed understanding of the cause of a problem is of hardly any help in framing a solution to it. If you have established lymphoedema for example (and over 120 million people do), there is little help to be had from modern physiology – genomic, proteomic or otherwise. On the other hand, a sound surgical approach, thorough anatomical knowledge and some straightforward, old-fashioned applied physiology can help quite a lot.

The editors of this book – two professors of surgery and a professor of medicine, each of whom has made substantial contributions to the field – are to be congratulated on producing a readable, well-referenced, wide-ranging and authoritative text which will be valued by a diverse readership.

John A Lee

Peptic ulcer: rise and fall

Wellcome witnesses to twentieth century medicine, volume 14. Edited by DA Christie & EM Tansey. The Wellcome Trust, 2002. 143 pp, £10.00 plus postage. ISBN 0 85484 084 2

The series of Wellcome witness seminars have been organised to illuminate recent medical history by bringing together people who were involved with a particular issue so that they can 'discuss, debate, agree or disagree about their memories'. The results, one of which is represented by this volume, are not textbooks, but nevertheless make fascinating reading for anyone with a bit of background knowledge on the subject under discussion.

Peptic ulcer is almost shocking for the succession of aetiological theories and associated treatments which have come and gone in a relatively short time. The disease itself seems to have come and gone as well, apparently being relatively rare before the twentieth century, reaching a peak around about 1950 when it affected perhaps 10% of men, and subsequently declining again for reasons which are not entirely clear. Haemorrhage and perforation were common complications, not infrequently fatal. Even within the last 30 years 'stress' was thought to be an important causative factor. Gastric acid production was also important, since patients with atrophic gastritis and little acid secretion did not develop ulcers. When 'medical' treatment with antacids, diet or bedrest failed (as it often did), there was a whole variety of surgical options, some more heroic than others and none of which were entirely satisfactory. Then, suddenly, a whole medical and surgical era came to an end with the introduction of H2 receptor antagonists in the 1970s. And then, just as everyone was getting used to the fact that there was now an established treatment for peptic ulcer, albeit one that required continuing medication, there was another dramatic twist. In the early 1980s peptic ulcer turned out to be an infectious disease. The causative organism, *Helicobacter pylori*, is a bacterium with an unusual environmental niche and a predilection for damaging the stomach's self-defense mechanism, causing it to locally dissolve itself. Pathologists had been seeing the bug in histological sections for years, but ignoring it as 'contamination' - a good example of seeing but not understanding.

Those of you looking for a Nobel prize take note, there are other common diseases which currently have complicated causative theories, but which may also turn out to be at least partly infectious in origin. Pre-eminent among these is arterial atheroma - the main cause of heart attacks and strokes. In thirty or fifty years time, Volume n of the witness series may be devoted to that story. But in the meantime, the ebb and flow of the story of peptic ulcer, told by those who lived it, is an absorbing testament to the winding and often unpredictable path of medical science.

John A Lee

Royal Society elections

John Robson has recently been appointed a Fellow of the Royal Society, and Denis Baylor a Foreign Member.

Member's success

Dr Stephen Gomez, Principal Lecturer in Human Physiology at the University of the West of England, has won a prestigious national teaching fellowship prize of £50,000, awarded by the National Teaching Fellowship Scheme, which was set up in 2000 to reward excellence in teaching and learning. Stephen has a track record of innovative physiology teaching and has introduced credit-rating of placement learning.

FORTHCOMING PHYSIOLOGICAL SOCIETY MEETINGS

2003
Manchester 9 – 12 September
Cambridge 17 – 19 December

2004
Glasgow 29 – 31 March
Babraham Institute, Cambridge – 1 May
Cardiff 6 – 7 July
Cork 1 – 3 September
King's College London 16 – 18 December

2005
Bristol 20 – 22 July

IUPS 2005 – 35th CONGRESS OF THE INTERNATIONAL UNION OF PHYSIOLOGICAL SCIENCES

San Diego, CA, USA
31 March – 5 April, 2005

IUPS 2005 is being organised by the six member societies of the US National Committee of the IUPS, the American Physiological Society, the Society for Neuroscience, the Microcirculatory Society, the Society of General Physiologists, the Biomedical Engineering Society and the Society for Integrative and Comparative Biology, under the auspices of the US National Academy of Sciences.

http://www.IUPS2005.org

THE BIOLOGY OF CHLORIDE

Woods Hole, USA
3 – 7 September, 2003

57th annual meeting and symposium of the Society of General Physiologists.
Further details from: http://www.emory.edu/CELLBIO/SGP/sgp.htm

MOLECULAR TECHNIQUES FOR LIFE SCIENCES

20 – 22 August, 2003

PCR Theory and Practice
A three day workshop to familiarise participants with this essential technique.
Price: £425

8 – 12 September, 2003
26 – 30 January, 2004

Manipulating Nucleic Acids
A five day practical workshop to introduce participants to techniques used in molecular biology investigations and to facilitate development of core molecular biology skills
Price: £715

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THE CONGRESS OF THE LATIN-AMERICAN ASSOCIATION OF PHYSIOLOGICAL SOCIETIES (ALACF) AND THE BRAZILIAN PHYSIOLOGICAL SOCIETY (SBFIS)

Ribeirao Preto, State of Sao Paulo, Brazil
1 – 4 September, 2003

INTERNATIONAL WORKSHOP IN NEUROSCIENCE

Bucharest, Romania
23 – 25 September, 2003

Ischemia/Hypoxia in the Brain
Organised by the Physiological Society and the National Neurosciences Society of Romania
Online registration: http://www.snn.ro/workshop2003

FIRST INTERNATIONAL CONFERENCE OF THE NATIONAL NEUROSCIENCES SOCIETY OF ROMANIA

University of Medicine and Pharmacy, Bucharest, Romania
26 – 27 September, 2003

Registration: www.snn.ro

BIOSCIENCE 2004 - FROM MOLECULES TO ORGANISMS

SECC, Glasgow, UK
18 - 22 July 2004

Poster abstract deadline: 23 April 2004
Early registration deadline: 18 May 2004
www.BioScience2004.org

Noticeboard

Notices for the Winter 2003 edition of *Physiology News* should reach the Publications Office (lrimmer@physoc.org) by 2 September, 2003.

Please note that whilst members are welcome to advertise relevant events in *Physiology News* and on the Society's website, advertisements via email will be restricted to events sponsored by the Physiological Society.

Clockwise from top: Radar station 305 at Mwananoia (Goodenough Island, New Guinea), where Bernard Katz served as the first commanding office from October 1942 to March 1943. Pilot officer Bernard Katz on the beach where a landing was made to reach Mwananoia. Portrait of Bernard Katz by Jenny Hersson-Ringskog (1997). Work at Plymouth Marine Laboratory in 1948 with Alan Hodgkin led to the descovery that the overshoot of the action potential results from an influx of sodium ions. Recordings of miniature (top) and evoked (lower) end-plate potentials (Fatt & Katz 1950, *Nature* **166**, 597). Maps showing the location of the radar station.