

PN

Physiology
News

Issue 96 / Autumn 2014

Are my genes to blame
when my jeans don't fit?

Obesity – a global
health crisis

Appetite control and
exercise: not just energy-in
and energy-out

Obesity special issue

Ageing & Degeneration: A Physiological Perspective

10-12 April 2015

Royal College of Physicians
Edinburgh , Scotland



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edition of *Physiology News*

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Physiology 2015

6 - 8 July 2015

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Registration Opens

1 January 2015

Abstract Submission

1 March - 31 March 2015

www.physiology2015.org



Physiology News

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New Age Physiology



Richard Vaughan-Jones

President

I remember as a child in the 1950s, hearing about the ages of civilisation. Grown-ups talked about the stone-age, iron-age, and later industrial age. These sounded grand and mysterious. 'So what age are we in now?' I once asked my mother. She looked blank, and then responded that we lived in a modern age, one of motor cars, aeroplanes and science. Clearly that was a brush-off, so that she could continue compiling her grocery list. But I have often thought how I myself might answer, especially now, as I take over from Jonathan Ashmore as President of The Physiological Society. We seem to have passed through a series of 'post' eras, ones not categorised with a particular moniker, but which have followed on anonymously from well-defined, previous eras. So we have been post-modern, post-industrial and, in the life sciences and medical sciences, we are post-Darwinian, post-molecular and post-genomic. We can see where we have been but, apparently, we are not prepared to commit to where we are going, or we would surely give it a name. I would suggest that in medical and life sciences, we are entering a renaissance in physiology. This won't always be branded as such, given that physiology now comes in many guises. But we have been there already, and we are rising again.

The 19th century witnessed the first age of physiology, and its formulation as the 'science of life'. Its principles were enshrined in 1876, by the founding of The Physiological Society, and by the scientific articles published in its journal (*The Journal of Physiology*). They were practised throughout the 20th century, giving us descriptions of hormones, receptors, membrane transporters and channels, action potentials, synapses, neurotransmitters, nervous reflexes, cell motility, contraction, secretion, integrated cellular and organ-system regulation, and all the trappings of biochemistry, biophysics, neuroscience,

pharmacology and systems biology, plus a legion of other biomedical and clinical sciences. The list is by no means comprehensive, but it serves to illustrate the breadth of the subject. It also illustrates that our understanding, for example, of how the human body operates in health and disease, requires insight not only into its individual components, its genes and expressed proteins, but also into how these components are orchestrated *in-vivo*. Such interaction is complex, often resulting in counter-intuitive biological behaviour. And this leads us to the resurgence of physiology in the 21st century, the second age. This is being driven partly by the massive advances that we have witnessed in molecular genetics. Genomics and proteomics highlight fundamental components of life, but physiology is required to understand their interaction, and thus the dynamics of life. Physiology elucidates function. The principles of physiology have never been more in demand.

And what will this 21st century physiology look like? Multi-disciplinary, multi-departmental, international, it is already practised by life scientists, medical researchers and clinicians. It is drawing on major technical advances in imaging, from nano- to whole-body scale. It embraces molecular, genetic, cellular, biophysical and clinical techniques, as well as sophisticated mathematical modelling, and even the insights of evolutionary biology. But above all, physiology relies on a recognition that it is a coherent and vibrant scientific discipline. And this is why The Physiological Society is as important now as at its inception in 1876.

And The Society itself is undergoing a renaissance. Our annual scientific meetings are in excess of 1,000 delegates, this year's (July 2014) being at the Queen Elizabeth Conference Centre in London, opposite Westminster Abbey, and a stone's throw from the Houses of Parliament. Last year, The Society successfully sponsored the International Union of Physiological Sciences in Birmingham, a 4-yearly international event that attracted more than 3,000 delegates. In 2015 we will be in Cardiff, and 2016 in Dublin. The Society is also organising cross-cutting Topic Meetings on issues of increasing scientific importance, which embrace multiple research areas. For example, September saw a meeting in Newcastle on the physiology of obesity, while in April 2015, there will be a Topic Meeting on ageing and degeneration. But more specialised thematic scientific meetings are also to be encouraged, in order to promote physiology more fully. As part of its renaissance, The Society has, for the first time in its history, purchased and refurbished new premises in London: Hodgkin Huxley House (H³, for short). These contain a lecture theatre

and conference rooms, so that smaller more intimate scientific meetings for up to 70 people can be held on site.

The move to our H³ headquarters, which was led by my predecessor, Jonathan Ashmore, and by the Society's chief executive officer (CEO), Philip Wright, has now been successfully concluded. Jonathan's term of office has also led to the founding of a new online, open-access journal, *Physiological Reports*, run in collaboration with the American Physiological Society. This takes its place alongside The Society's *Journal of Physiology* and *Experimental Physiology* as an important scientific voice for the physiological community. All the indications are that it is becoming established as a key online journal, notable for its rapid response and high quality of science.

So, The Society is now in a strong position to continue doing what it was set up for, and that is promoting physiology for its members and the public. The clear emerging need for physiological science must be translated into Society support, wherever possible, for those who practise, both new recruits and more established personnel. Issues of Society membership, our infrastructure for communicating with members, and a clear provision of news and information through this magazine, through our online newsletters, and our Society website, will be a high priority during my presidency. We have reorganised our central headquarters, and our academic publications. Now it is time to get back fully to the business of addressing the science. Our aim must be to open The Society more to its members. Do please use H³ for scientific conferences. Do please get involved in our network of Society representatives. Do contact us: me, our newly elected Deputy President (Professor David Eisner), our Council members, our CEO, and our local representatives. Use our email and social media. At a time when demand for physiology is rising, but when named Departments of Physiology in academic and scientific institutions are declining, it is more important than ever to use The Society as a central hub for activity. Use it as a focal point for networking, collaboration, sharing research news, and for promoting the importance of our subject. Indeed, our outreach and policy activities include, not only schools and universities but also other learned societies and government. As President, I hope to facilitate these aims, assisted by our staff, Council and members. I thank my predecessor Jonathan Ashmore for so assiduously bringing The Society to this auspicious moment. The period ahead must not be another 'post' era. Rather it should be an age of original and productive physiology.

Annual General Meeting 2014

The 2014 AGM took place during Physiology 2014 at the Queen Elizabeth II Conference Centre, London, on Tuesday 1 July with over 70 members attending. Trevor G Smart, Schild Professor of Pharmacology at University College London, chaired the meeting.

Richard Vaughan-Jones, Professor of Cellular Physiology at Oxford University, succeeded Jonathan Ashmore as The Society's President. Richard gave a vote of thanks and praised Jonathan Ashmore for his energy, enthusiasm and empathy, guiding The Society through a number of significant events, including the move to Hodgkin Huxley House, the successful renegotiation of the publications contract and the hosting of the IUPS Congress in 2013.



Trevor G Smart

Ken O'Halloran succeeded David Wyllie as Meetings Secretary while Prem Kumar succeeded Mike Shipston as Chair of the Publications Committee.

Philip Aaronson, Deborah Baines and David Eisner were elected to Council as Trustees and Directors of The Society for a four-year term, with David becoming Deputy President.

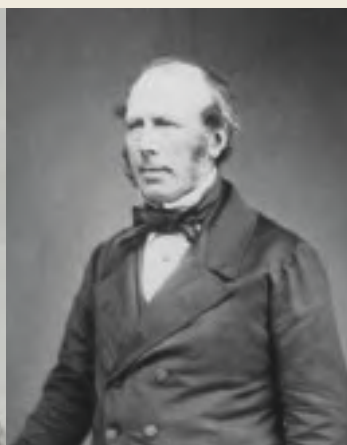
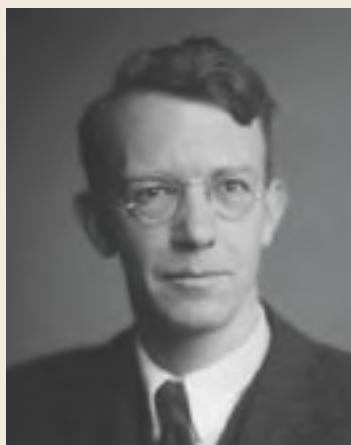
The Society is delighted to welcome 10 new Honorary Members, elected for their outstanding contribution to The Society



Members at the AGM

and/or the science of physiology:

- Jonathan Ashmore
- Tony Gardner-Medwin
- Max Headley
- Martin H Johnson
- Jere H Mitchell
- Harald Reuter
- James Rothman
- Randy Schekman
- Thomas Sudhof
- Tilli Tansey



Who are your scientific grandparents?

David Miller

The History & Archives Committee is instigating an online Physiology 'Family Tree'. Many will be aware of such 'trees' hosted at www.academictree.org. Here one can see scientific 'families' as they have grown through generations of doctoral supervisors, collaborators and shared colleagues.

Such trees already exist for e.g. Anthropology, Philosophy, Physics, Chemistry, Evolutionary Biology, Developmental Biology, Cell Biology and Neuroscience. The last in particular already

includes many of the founding fathers (and a few mothers) of our discipline.

At the recent Physiology 2014 meeting, nearly 100 members completed simple forms to help to provide the start for the Physiology tree. Together with the cross-connections from Neuroscience and other trees, this can soon grow into a large resource. Apart from simple human interest, such trees can help to reveal the 'sociology' of science: who worked with whom, when and where. This can throw new insights into how techniques and ideas – as well as the scientists themselves – first came together.

When the skeleton is ready to be made available online, we will announce it on The Society's website. Then, as with the existing trees, the resource will be open-access, enabling anyone to edit, revise and enhance the information available. Fortunately, the software running academictree.org takes care of all the rest.

(For the curious, the images above are of: George Lindor Brown, John Stanley Gardiner, William Sharpey and Marthe Vogt.)

The Science of Life: How Your Body Works competition 2014

We are delighted to announce the winners of our second ever nationwide school research competition, The Science of Life: How Your Body Works. The final took place on 30 June at Physiology 2014. As with the first competition (The Science of Sport: How to Win Gold) back in 2012, we invited 16- to 19-year-olds to complete a physiology research project of their own (either alone or in groups) and then present their findings to The Society. This time, however, we expanded the theme to welcome projects in all areas of physiology, and we were pleased to receive a wide variety of submissions in topics from neuroscience to nutrition.

Fourteen entries altogether reached the final and presented their projects as posters to a panel of judges at the Main Meeting. The judges were really impressed with the quality of projects this year, one of which they felt was particularly outstanding: the gold prize therefore went to Eva Harris from Kent College, Canterbury for her excellent project on the effects of breakfast cereals with different glycaemic indexes on cognitive performance in the morning. Eva was delighted with this result and said, 'When I first heard about this competition I had a feeling that it would be something special and that feeling was definitely right! It was a fantastic experience which has given me a real taste of what scientific research could be like. I did not expect to win, but I was delighted and I am now considering a career in medical research.'



Gold, Silver and Bronze winners of the Science of Life: How your body works competition

Silver prize went to a team of students from Seven Kings High School in Essex, while bronze prize was awarded jointly to a team from Tiffin School in Surrey and another team from Langley Grammar School in Berkshire. Each of the winners received a medal, certificate and further prizes as a reward for their achievement. Gold prize winner Eva Harris, for example, will visit the Centre of Human and Aerospace Physiological Sciences at King's College London. Details of other prizes are available at www.understanding-life.org

We would like to congratulate all the winners and thank everyone who took part, including the judges and those who gave up their time to mentor the students throughout their projects for the competition.

2014 Rob Clarke Awards



The 2014 Rob Clarke Award winners alongside members of the judging panel

We are also pleased to announce the winners of the 2014 Rob Clarke Awards, which recognise excellence in undergraduate physiology research. Nineteen finalists were selected for an Abstract Award and invited to present a poster to a panel of judges at Physiology 2014 on 1 July. Of these, 11

Presentation Awards were given to the following individuals (the top 3 in particular were considered to be outstanding amongst the group):

- Dhruva Biswas (University of Cambridge)
- Lisa Kafer (University of Dundee)
- Cáelán Taggart (University of Dundee)
- Carolyn Dales (University College London)
- Charlotte Horne (University of Bristol)
- Kazi Sultana Jahan (St George's, University of London)
- Jennifer Kwan (University of Leicester)
- Emily Prpa (University of Bath)
- Anita Sagoo (University of Portsmouth)
- Andy Shaw (University of Stirling)
- Thomas Topham (Brunel University)

Congratulations to all the winners, and a huge thank you to all the judges for their time and assistance in reviewing the entries.

Physiology Feed

Bringing you snippets of the latest intriguing research

Male experimenters stress rodents

Olfactory exposure to human males and other unfamiliar mammals (including clothes or bedding materials) induce physiological stress responses that results in stress-induced analgesia. Therefore an experimenter's sex can affect apparent baseline responses in behavioural testing.

DOI: [10.1038/nmeth.2935](https://doi.org/10.1038/nmeth.2935)

First mapping of the human proteome

Two independent teams have drafted the first maps of the human proteome by mass spectrometry analysis of various tissues, body fluids and cancer cell lines; 193 novel proteins from the 'non-coding' regions of the genome have been discovered.

DOI: [10.1038/nature13302](https://doi.org/10.1038/nature13302)

DOI: [10.1038/nature13319](https://doi.org/10.1038/nature13319)

Childhood trauma and stress permanently affect DNA

A correlation has been discovered between childhood exposure to traumatic events within the family and telomere length. Children experiencing stress, in particular girls, had significantly shorter telomeres, which is hypothesised to be a predictor of negative health outcomes throughout life.

DOI: [10.1542/peds.2013-3415](https://doi.org/10.1542/peds.2013-3415)

Tibetan high-altitude adaptation due to extinct human species

Introgession of DNA from Denisovans (~40,000 years extinct), in particular a EPAS1 variant, confers increased haemoglobin and red blood cell production to the Tibetan population, thus allowing adaptation to the ~40% lower atmospheric oxygen pressure of the Tibetan plateau.

DOI: [10.1038/nature13408](https://doi.org/10.1038/nature13408)

Tracking individual cells throughout embryonic development

This study shows tracking of up 20,000 cells in fruit fly, zebrafish and mouse embryos through to the advanced stages of development. Using a simultaneous multi-view light sheet microscope they could reconstruct cell lineages from four-dimensional, terabyte-size image data sets with 97% accuracy.

DOI: [10.1038/nmeth.3036](https://doi.org/10.1038/nmeth.3036)

continues overleaf

Physiology Feed

Bringing you snippets of the latest intriguing research

Consciousness on/off switch

Electrical stimulation of a patient's claustrum while undergoing routine deep brain electrode recording for epilepsy revealed consciousness could be reversibly disrupted. The stimulation reproducibly resulted in unresponsiveness, amnesia and arrest of volition behaviour.

DOI: 10.1016/j.jybeh.2014.05.027

Neuron subset essential for asthma attacks

Researchers have discovered that silencing a specific population of sensory neurons in the vagal ganglia abolishes asthmatic hyperreactive broncho-constrictions in mice. These TRPV1 expressing neurons represent an attractive therapeutic target physiologically dissociated from the immune component of asthma.

DOI: 10.1073/pnas.1411032111

Genetic link to autism subtype

For the first time, a variation in a gene has been linked to a subtype of autism. Disruptive CHD8 mutations define a subtype of autism early in development. Zebrafish with the CHD8 mutations recapitulate the human phenotype and comorbidities.

DOI: 10.1016/j.j.cell.2014.06.017

Erase and restore memories

Engineered inactivation and reactivation of a memory (foot shock) has been achieved with optogenetic delivery of long-term potentiation and long-term depression conditioning in rats, supporting a causal link between these synaptic processes and memory.

DOI: 10.1038/nature13294

Epigenetic changes can drive cancer

Cancer has long been viewed as a genetic disease. However this study provides the first *in vivo* evidence that epigenetic alterations alone can cause cancer. Engineering mice to be susceptible to p16 hypermethylation increased the incidence of spontaneous cancers and reduced survival.

DOI: 10.1172/JCI76507

If you spot some interesting research that you'd like to share with your fellow Members, please send it to us at magazine@physoc.org

Policy Focus

Engaging with Parliamentarians launched!

The policy committee launched its 'Engaging with Parliamentarians' programme at a lunch reception, held on 30 June in the House of Lords. Andrew Miller, MP, who chairs both the Commons Science and Technology Select Committee and Parliamentary and Scientific Committee, delivered an address to approximately 50 Society members who were in attendance. Mr Miller provided a brief overview of science in parliament and then answered questions from the audience. The Society sincerely thanks Mr Miller for his talk and The Baroness Golding for hosting the event. The next stage of the programme is a training day, to be held at Hodgkin Huxley House in September, which will be reported in a future issue of *Physiology News*.



Physiologists engage with MPs

David Cameron names new science and education ministers

The July cabinet reshuffle resulted in a number of ministerial changes of note for The Society. Dr Greg Clark has replaced David Willetts as the Minister for Universities and Science. Dr Clark, who has a PhD in economics, will be combining this role with his previous position as Minister for Cities and Constitution. George Freeman, having previously been a Life Science Adviser to the Government, has been made the Minister for Life Sciences. It is a new ministerial position, which will sit jointly between the Department for Health and Department for Business, Innovation and Skills. In education, Nicky Morgan has replaced Michael Gove as the Secretary of State.

Society responds to Home Office consultation on section 24

The Society responded to a Home Office consultation on the review Section 24 of the Animals (Scientific Procedures) Act 1986. Section 24 prohibits the release of information relating to animal research gathered by the Home Office under its legislative duties. The response called on the Government to ensure that people, places and intellectual property were provided with suitable protection following the review of Section 24. The Society responded to this consultation through the UK Bioscience Coalition and also submitted a supplementary submission with the British Pharmacological Society. The responses can be found on our website – www.physoc.org/our-impact

If you are interested in these or any other policy related issues please contact us via policy@physoc.org



Obesity – a global health crisis

Hannah Brinsden

World Obesity Federation

Barely a generation ago, our primary concern about global nutrition was linked to underweight, undernourished individuals. Today, whilst these problems continue to persist in many parts of the world, we are also faced with new health concerns about the rapid rise in obesity and non-communicable diseases (NCDs) such as heart disease, diabetes and several diet-related cancers. Worldwide obesity has nearly doubled since 1980, there are more overweight adults than underweight ones, and it is now recognized as one of the most important public health problems facing the world today (World Health Organisation, 2013). Once associated with developed countries such as the USA, Australia and Western Europe, obesity and NCDs are increasing in every corner of the world, and most rapidly in low and middle income countries such as those in the Middle East and Latin America. Obesity affects adults and children, men and women, rich and poor and high and low income countries.

In response to this growing burden, the World Health Organisation (WHO) has set a target to halt the rise in obesity by 2025 (World Health Organisation, 2011) and there are many other policies and commitments to tackle this problem. However, to date, no country has yet been successful in reversing the rise in obesity. That is why The Physiological Society's focus on obesity for 2014 is so important and relevant today.

Obesity and health

Obesity is a major cause of morbidity, disability and premature death, compared to smoking because of its associated disease burden and impact on population health. In 2008, around 1 in 4 adults worldwide were overweight (1.5 billion adults), of which 200 million men and nearly 300 million women were obese (International Association for the Study of Obesity).

Body mass index (BMI) is a strong predictor of mortality among adults. Worldwide, the number of deaths from high BMI and physical inactivity was 6.56 million in 2010, more than that from tobacco (Lozano *et al.*, 2012). Overall, moderate obesity (BMI 30–35 kg/m²) has been shown to reduce life expectancy by an average of three years, while morbid obesity (BMI 40–50 kg/m²) reduces life expectancy by 8–10 years. This 8–10 year loss of life is equivalent to the effects of lifelong smoking (Lancet, 2009). In the UK, obesity affects one in three adults in late middle-age (around 55–70 years old), and morbid obesity affects one in every 25 adults of this age (Health & Social Care Information Centre, 2014).

Obesity increases the risk of a wide range of chronic diseases. High BMI is thought to account for 60% of the risk of developing type 2 diabetes and 20% of hypertension and coronary-heart disease. There is also a strong link between body fatness and gall bladder, kidney, colorectal, ovarian, oesophagus, postmenopausal breast, pancreatic and endometrial cancers (World Cancer Research Fund International, 2014). This relationship is most likely due to the increase in the hormones insulin and leptin which is commonly seen in obese adults and thought to promote the growth of cancer cells. Other co-morbidities of obesity include raised cholesterol, fatty liver disease, sleep apnoea, heartburn, osteoarthritis and depression.

Of particular concern is the rise in obesity in vulnerable groups such as children and pregnant women. Global figures suggest there are more than 100 million obese women of child bearing age, with a further 250 million who are overweight (International Association for the Study of Obesity). Maternal obesity during pregnancy poses risks for both fetus and mother pre- and post-pregnancy. Obesity in pregnancy is associated with an increased risk of miscarriage, gestational diabetes, hypertension, pre-eclampsia, high risk labour, haemorrhage and maternal death. Maternal obesity can increase the risk of fetal distress, still birth (Schumann *et al.*, 2014) and a 'large for gestational age' birth, which

Defining overweight and obesity

Overweight and obesity are measured and identified using body mass index (BMI).

BMI (kg/m²) = weight (kg) / height² (m)

The World Health Organization defines weight categories as follows:

Classification BMI (kg/m²)

- Underweight <18.50
- Normal weight 18.50–24.99
- Overweight ≥25.00
- Pre-obese 25.00–29.99
- Obese ≥30.00
- Class I or moderate obesity 30.00–34.99
- Class II or severe obesity 35.00–39.99
- Class III, very severe or morbid obesity ≥ 40.00

can increase the likelihood of labour and birth complications. High gestational weight gain can increase BMI of an infant later in life.

Over 200 million schoolchildren worldwide and more than 40 million children under the age of five were overweight in 2010 (International Association for the Study of Obesity). Childhood obesity is associated with an increased risk of disease later in life and it has been predicted more than three quarters (77%) of obese children become obese adults (Freedman *et al.*, 2001). Obese children have been found to have increased risk of type 2 diabetes, hypertension, raised blood cholesterol, metabolic syndrome and fatty liver disease (Lobstein & Jackson-Leach, 2006; Reilly *et al.*, 2003).

The economic and social burden of obesity

Obesity presents a significant financial burden to individuals, health services and the economy, both directly and indirectly. It has been estimated that the average obese person costs 36% more in medical care than healthy weight people (Thompson *et al.*, 2001). Direct medical costs include the preventative, diagnostic and treatment services related to overweight and associated co-morbidities, while indirect costs include income lost from decreased productivity, reduced opportunities and restricted activity, illness, absenteeism and premature death. The cost of obesity is rising with estimates suggesting it was responsible for about 9% of total healthcare spending in 2003, on average across OECD countries, up from just 5% some 30 years earlier. In the USA it now exceeds 16% of the national health care budget (OECD, 2011). In the UK, the healthcare costs attributable to overweight and obesity are projected to double to £10 billion per year by 2050 with the wider costs to society and business estimated to reach almost £50 billion per year (Butland *et al.*, 2007).

There is also a problem of prejudice against obese individuals resulting in issues of stigma, both within the general population and within healthcare services. This in turn can lead to depression and low self-esteem, which can affect an individual's quality of life, mental health, educational achievement and

employment prospects. Prejudice found among health service staff can also put obese people off seeking treatment or continuing with treatment they have started.

SCOPE

Specialist Certification for Obesity Professional Education

is an online education package offered by the World Obesity Federation designed to improve health service delivery through training of healthcare professionals.

More information can be found at www.worldobesity.org/scope

The multiple drivers of obesity

The UK government's 2008 Foresight report described the 'complex web of societal and biological factors that have, in recent decades, exposed our inherent human vulnerability to weight gain' (Butland *et al.*, 2007). According to the 'thrifty gene hypothesis' the genes that helped our ancestors survive are the same genes that are causing obesity. While there is a direct link between genes and obesity in conditions such as Bardet-Biedl syndrome and Prader-Willi syndrome, many obesity genes

are only expressed in the presence of obesity-promoting behaviours such as sedentary behaviour and/or high energy intake, and the environments that promote such behaviours.

Unfortunately the lack of a single definitive cause of obesity means there is no quick fix solution. We must therefore work together, in our respective areas whether that is in research, policy, prevention or treatment, to try to get to grips with this epidemic. Preventing obesity through policies that address the environmental drivers, particularly food environments that promote diets high in fat, sugar and salt (Monteiro, 2011, Frazao, 1999) is essential, but health care professionals also play an important role in providing patients who are either already overweight or obese, or at risk of becoming overweight, with advice on weight loss programmes and treatment options such as surgery and drugs, something that World Obesity's education programme SCOPE is working to support health professionals with.

It is not impossible to tackle this health problem – weight loss of just 10% can bring about significant improvements in co-morbidities – but we all need to do our bit and act now.

More information about obesity and the World Obesity Federation can be found at www.worldobesity.org, or why not follow us on twitter @worldobesity

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Obesity outreach activities

Anisha Tailor

Outreach Officer,
The Physiological Society

Take a moment to ponder that common cliché 'one size fits all'. There are few occasions, if any, when we can honestly say that this phrase holds true. Exercise, diet, hormones, genes – the physiology of obesity is certainly an area where diversity reigns supreme.

For 2014, The Society has shone the light on this controversial topic, and through a united front we have worked to clear up myths and misconceptions, by highlighting the physiological causes and consequences of this global epidemic.

Obesity is becoming a growing health concern in the UK. A quick Google of the terms 'obesity', 'fat' and 'overweight' and you are greeted with over 14,100,000 results. With the internet being one of the main sources of the information we consume, it is easy to see how misinformation and confusion can spread. As part of our themed year we have aimed to create a dialogue around the physiological side of obesity through a range of outreach and public engagement events.

We started the ball rolling in February with a public lecture from Alexandra Blakemore. The Professor of Human Molecular Genetics at Imperial College London joined us in our new home, Hodgkin Huxley House, to discuss a subject which is often met with public vitriol, the relationship between genes and obesity.

While sedentary lifestyles and overindulgence get the brunt of the blame for increasing waistlines, the genetic side remains relatively in the background. Alex, however, is a firm believer that genes are indeed an extremely important factor, and that 'understanding the genetics of obesity will help us deal with a growing and very important problem'.

In her lecture, entitled 'Genetics and the prospect of personalised medicine for obesity',

Alex highlighted twin studies as an indication of the link between obesity and genes: identical twins are far more likely to both be obese than non-identical twins. So why is there so much doubt, 'how does it make logical sense to say our height is controlled by our genes but not our width?' Alex went on to discuss her work in finding and investigating the genetic difference between individuals which plays a role in adiposity and how this information can be used to inform a personalised route of care in dealing with the issue.

Our discussion on genes continued in April at Edinburgh International Science Festival. This time Colin Moran, lecturer at Stirling University, was its advocate. Colin was joined by Julian Mercer (University of Aberdeen), Tony Goldstone (Imperial College London) and Naomi Brooks (Stirling University) to explore the causes of obesity in our panel discussion 'Separating the fat from the fiction'. Over the 90 minutes session, each speaker took to the stage campaigning that their cause was the most important factor, and quizzing the audience along the way with the use of interactive voting buttons.

In June we attended Cheltenham Science Festival with our talk 'The BMI Lie'. Our speakers, Janice Thompson, Jason Gill and self-proclaimed lover of fat Jimmy Bell, discussed the pros and cons of using BMI as a measure of health. Our expert physiologists talked about how health risks varied between different ethnicities, and the risk factors associated with subcutaneous and visceral fat.

Alongside our adults' engagement we also took our theme to younger audiences. With a troop of knowledgeable volunteers, and three neatly packed boxes, we travelled to Birmingham for The Big Bang Fair, an annual event to promote science, technology, engineering and maths (STEM), and Cheltenham Discover Zone, a hands-on area of Cheltenham Science Festival.

Inside our boxes 'The Hungry Games' popped out, a collection of hands-on activities delving into the hormonal pathways behind appetite in the activity 'Look who's talking', energy



The Hungry Games at the Big Bang Fair

balance and weight management in 'It's balancing act', and a deeper look at how fat is distributed around the body, and the differences between 'healthy' and 'overweight' in our card game 'Play your BMI right'. Thousands of school pupils, teachers and parents engaged with our stand, questioning us on the use of hormones in diet drugs, and how a young Arnold Schwarzenegger could possibly be considered obese. 'The Hungry Games' still has another stop to make this year: it will be making its way up to Newcastle for our 'Fair of Physiology', a day of interactive science for local schools running alongside our Obesity Meeting in St James' Park, Newcastle-upon-Tyne.

It's been a fantastic year, and we would like to thank all of our hard-working volunteers, our expert speakers, and our very knowledgeable advisers. We hope next year's programme of events will be just as exciting as we tackle our 2015 theme 'Understanding Ageing'.

The Society has been working with other organisations to develop a public programme of outreach events for our themed year of 'Understanding Obesity'. We would like to thank The Biochemical Society, The Nutrition Society, the University of Essex, Imperial College London, Heriot Watt University and the University of Stirling.

Alexandra Blakemore's full lecture can be found on The Physiological Society's YouTube Channel.

Are my genes to blame when my jeans don't fit?

Giles Yeo

The MRC Metabolic Diseases Unit,
Addenbrooke's Hospital, UK

Just recently a major supermarket chain opened an 'express' store at the hospital where I am based, one of these places that sells primarily convenience food and drink. I was there one day getting a sandwich for lunch, with what appeared to be everyone else in the hospital, and was standing in line behind a nurse who had, clutched in her hand, a salad and a yogurt. This nurse had clearly started her foraging expedition with all the best will in the world, and if the cash till had been right there, she would have made it out of the shop with an undeniably healthy lunch. However, as the line snaked in Disneyland-like fashion inexorably towards the checkout, so began the obstacle course of chocolates, candies, crisps and other temptations that are located, as is typical, close to the tills. The nurse looked longingly at every treat but managed to shuffle past each time. This must have happened 10 or more times. In my head, I was cheering her on: 'Come on! You can do it!' Finally she made it to the till, and as her guard dropped, the cashier pounced with a deadly offer: 'Would you like some freshly baked cookies? Two for one today?' And the battle was lost. The nurse walked out the shop with almost 800 extra calories in cookies.

Since time immemorial, the control of food intake and body weight has been thought to be simply an issue of self-control and willpower. Gluttony is, after all, one of the 'seven deadly sins'. So as obesity has become an increasing public health problem, reaching epidemic proportions in most developed and emerging economies, society in turn blames those overweight and obese for a lack of moral fortitude. 'The obese only have themselves to blame, all they have to do is to eat less...' so the argument goes.

From a thermodynamic standpoint, this view is of course quite accurate. Body-weight is


clearly a balance between energy intake and energy expenditure. Thus, the only way to gain weight is to eat more than you burn, and the only way to lose weight is to eat less than you burn. There, in one succinct statement, is the cause and cure of the obesity epidemic. However, this sage piece of advice that your grandmother could have given you is clearly not working. The story above of the foraging nurse is by no means unique. A far more complex and interesting question to ask is *why* some people eat more than others. Few would dispute that the obesity epidemic has been driven by lifestyle and environmental changes. However, individuals respond differently to these 'obesogenic' environmental changes and this variation in response has a strong genetic element underlying physiological variations. Indeed studies of BMI (body mass index; weight in kg/height in m²; a correlate of body fat mass) correlations of monozygotic, dizygotic, biological and adopted siblings reveal heritability of fat mass to be between 40 and 70%. Consequently, genetic approaches offer an effective tool for characterising the molecular and physiological mechanisms of food intake and body weight control, and allow us to understand how these may become defective in the obese state.

The control of energy balance involves a homeostatic feedback control circuitry, whereby peripheral signals communicate energy availability to the central nervous system (CNS), and hypothalamic circuits drive appropriate feeding and fuel partitioning responses. It was first proposed in the 1950s that circulating signals generated in proportion to body fat stores influenced food intake and energy expenditure in a coordinated manner to regulate body weight. However, it was not until the cloning of leptin in 1994 that the molecular basis for this homeostatic control was identified. The study of extreme phenotypes in both mice and humans has subsequently identified a number of genes that when mutated cause severe obesity. Although relatively rare, these monogenic disorders indicate a fundamental failure of the mechanisms of energy homeostasis, and together with genetically

modified mouse models, have illuminated the critical role that these molecules play in the physiological control of food intake and bodyweight. We now know that peripheral homeostatic regulators of energy balance can be broadly divided into (a) fat derived hormones such as leptin responsible for signalling long-term energy stores, and (b) gut-derived hormones, which regulate short-term control of food intake. These long- and short-term peripheral nutritional signals are sensed by the brain, in particular by the hypothalamus and the nucleus of the solitary tract in the brainstem, where they are integrated and acted upon to appropriately regulate food intake and energy expenditure

However, the major burden of disease is carried by 'common obesity,' which to date has resisted yielding meaningful biological insights. In contrast to the Mendelian obesity syndromes, common obesity is likely to have a 'polygenic' aetiology, with multiple variations each having a subtle effect. Only recently has the spate of genomewide association studies (GWAS) begun to reveal some of the genetic architecture underlying common obesity. Powerful though it has been, it is however important to consider the limitations of what GWAS can offer. GWAS is after all a gene agnostic approach. SNPs reaching the appropriate statistical threshold for a given phenotype or disease can appear anywhere in the genome, within, near or far away from any coding sequence. The current assumption that the closest coding region, which is sometimes hundreds of kilobases away, is the likely candidate is perhaps a reasonable first guess, but not necessarily true! Additionally, because of its 'hypothesis free' nature, the power of GWAS lies in uncovering potentially new biology that would not have been possible using a candidate gene approach. The problem with new biology, of course, is that, by definition, little or nothing at all might be known about the gene. Many 'scientist hours' are now being dedicated to turning these statistical hits into biological insight.

There is still the strongly held belief in many quarters that we are in full 'executive control' of our own eating behaviour; that the



environment is responsible for our shape and size, and that our genes, our 'nature', has minimal, if any, effect. However, it is crucial to remember that the drive to consume food is one of the most primitive of instincts to promote survival. It has been shaped by many millions of years of evolution and has provided living creatures with powerful and redundant mechanisms to adapt and respond to times of nutrient scarcity. Thus, I would argue that to be overweight in our current environment is indeed the natural, highly evolved even, response. The main issue is that the current environment, such as the lunch obstacle course faced by the nurse on a daily basis, in which energy dense foods and stimulatory food cues are ubiquitous, coupled with concurrent changes in lifestyle, is in dissonance with the millennia of austere surroundings to which we have adapted. This has consequently pushed obesity to become the serious problem it is today. I am fully aware that without this 'obesogenic' environment, most of us would not be overweight or obese; but to deny the central role that our genes have played in our response to this environment is unhelpful as we strive to tackle one of the greatest public health challenges of the twenty-first century.

A round up of obesity-related discussion at IUPS 2013, Birmingham

Caroline Wood

PhD student,
University of Sheffield, UK



In 2008, the World Health Organisation estimated that over 10% of the global adult population were obese. The corresponding rise in cardiovascular disease, Type 2 diabetes and cancer has caused this trend to be viewed as an 'epidemic' of great concern. By bringing together pioneering researchers working on the latest theories and techniques, IUPS provided a unique venue to engage with this issue. A wealth of symposia and keynote lectures explored the physiological impacts of the obese state and how current knowledge could be developed into clinical treatments.

Brown adipose tissue – a potential recruit for weight loss?

Not all fat, it seems, is bad for us. Whilst traditionally 'unhealthy' white fat acts as a reservoir of storage lipids, brown adipose cells are stimulated by the sympathetic nervous system to burn fat to produce heat (thermogenesis). Although once thought to be restricted to fetuses and newborns, modern scanning methods have shown that metabolically active brown adipose tissue (BAT) is also present in human adults, prompting researchers to question whether this could be manipulated to facilitate weight

loss. In her keynote lecture, *Brown adipose tissue: the mammalian prerogative*, Barbara Cannon, president of the Royal Swedish Academy of Sciences, outlined how BAT initially evolved as a strategy for cold-survival in mammals. Professor Cannon described how thermogenic ability depends on the mitochondrial channel UCP (thermogenin) and that knocking this channel out in mice prevents cold-stimulated BAT activity. Furthermore, mice lacking UCP are less able to maintain a steady weight on control diets and show greater weight gain on high fat diets, suggesting that BAT may protect against obesity. When radioactive glucose or triglycerides were fed to mice, BAT was found to clear 50 and 75% of these, respectively, implying that this tissue acts to counter hyperlipidaemia and hyperglycaemia, key features of the metabolic syndrome. This raises the question, is obesity promoted by a lack of BAT? Or does obesity reduce BAT because the body has greater insulation? In support of the former view, the UCP-1 channel has a polymorphic enhancer, with the so-called 'AA allele' promoting greater mRNA expression. Studies indicate that those carrying this allele burn more calories after a high fat meal and occupy the lowest quartile of population BMI.

The role of brown fat in weight control was discussed further in the symposium *What's hot in brown adipose tissue biology?* Dr Tim Schulz (German Institute of Human Nutrition) presented exciting evidence that white adipose tissue could be manipulated to take on a fat-burning brown phenotype. BAT and muscle cells derive from a common Myf5-positive progenitor, with lineage allocation determined by BMP7. White adipose tissue, on the other hand, originates from a separate Myf5 negative cell. In experiments where BMP receptor 1 α was deleted in mice, BAT was ablated yet the white fat remained unaffected. In these mice, sympathetic nervous stimulation to white fat deposits increased, causing them to adopt a brown phenotype. In addition, the mice were found to be resistant to diet induced obesity. Could inhibiting BAT progenitors be a mechanism to combat obesity in humans?

Besides cold temperatures, glucose uptake by BAT is also stimulated by insulin. Dr Saveiro Cinti (University of Ancona) outlined her work investigating how this process is affected by obesity. Her experiments compared the insulin responses of lean mice with individuals fed a high fat diet for 3 months to cause insulin resistance. In the obese animals, downstream insulin signal transduction in BAT (including the AKT pathway) showed reduced activity and insulin-promoted thermogenesis was inhibited. Furthermore, production of the energy storage molecule glycogen was suppressed, suggesting a mechanism by which BAT normally protects against hyperglycaemia. This was found to be due to reduced expression of the protein PTG (which stimulates the enzyme glycogen synthase) in the obese animals. In future work, Dr Cinti hopes to investigate the effect of obesity on other insulin-stimulated pathways, such as triglyceride production. Meanwhile, she described her other research interest: the role of endocannabinoids in regulating BAT. This relatively unexplored pathway uses signalling molecules similar to the active component of cannabis, tetrahydrocannabinol. These compounds are thought to be implicated in the metabolic syndrome due to the weight loss effects of the drug rimonabant. This acts as an inverse agonist of cannabinoid receptor 1 (CB1), i.e. it binds the receptor but induces an opposite effect to the natural agonist. Subcutaneous temperature probe implants indicate that the drug stimulates BAT thermogenesis, but Dr Cinti's studies found that inhibiting CB1 does not increase the basal glucose uptake in BAT. Specifically, CB1 inhibition increases glucose uptake in response to insulin and improves whole-body glucose-insulin sensitivity. As obesity and diabetes are often characterised by elevated cannabinoids and hyperactive CB1, this could indicate why insulin resistance develops in these conditions. Curiously, when BAT was denervated, Rimonabant failed to activate thermogenesis, suggesting that the endocannabinoid pathway is mediated by the sympathetic nervous system. Could this explain how drugs used to treat mental health that target the sympathetic nervous system can cause weight gain or loss? Although little known at



Delegates registering at IUPS 2013

present, endocannabinoids seem sure to assume a more prominent role in obesity research.

Intergenerational effects – blame the mother?

Is obesity simply the consequence of personal choice or do intergenerational effects play a role? This was explored in Monday's symposium, *Obesity: Intergenerational programming and consequences*. Professor Lucilla Poston (King's College London) opened the session by describing early studies on Pima Indians which found that individuals exposed to maternal diabetes *in utero* had a higher BMI than siblings born before the mother developed the condition. Since then, a wealth of studies have indicated that children have a 2- to 3-fold increased risk of becoming fat when the mother is overweight. Furthermore, a high pre-pregnancy BMI is also associated with birth defects and miscarriages. Professor Poston stressed, however, that this does not necessarily indicate a causal link and that confounding factors, such as poor household diets, should be taken into account. Nevertheless, siblings born following bariatric surgery in the mother show reduced incidence of obesity, improved lipid profiles and higher insulin sensitivity. Furthermore, 5698 genes are differentially regulated in offspring born before/after surgery. Professor Poston outlined her work

in the ongoing UPBEAT trial which is investigating the effects of intervention with a low GI diet and physical exercise in obese pregnant women. The results of this comprehensive study, which will have a sample size of 1546, will no doubt prove illuminating in the near future. Meanwhile, Poston's research on mice has provided insight into intergenerational mechanisms for obesity. In general, overweight mice give birth to fatter offspring which show an increased food intake and are resistant to the appetite-suppressive effects of the hormone leptin. Intriguingly, the mice showed an *increased* response to leptin-induced hypertension, showing that leptin resistance is selective. These offspring also exhibited a fatty liver phenotype reminiscent of humans with non-alcoholic fatty acid liver disease. Future studies will investigate whether these observations translate to humans born to obese mothers.

Professor Kimberley Bruce (The Scripps Research Institute) presented evidence that circadian rhythms may also be involved in intergenerational effects. Mice exposed to high fat diets in the uterus and postnatally showed dysregulation of key clock gene components, including *sirtuins* and *bma1*. Directly disrupting circadian rhythms in flies has been shown to have implications on diet and appetite. Knocking out the *cyc* clock gene, for instance, causes flies to consume larger meals but less frequently, implying an impaired ability to sense metabolic status.

The work of Dr Kevin Grove (Oregon Health and Science University) also suggests that nutrient signalling is disrupted in the obese state. His studies found that the activity of serotonin, a key regulator of energy homeostasis, was reduced in non-human primates exposed to high fat diets *in utero*. These primates also exhibited altered food preferences and a tendency to 'binge' when presented high-sugar food. More disturbingly, they also showed increased anxiety and withdrawal behaviour, similar to autistic-like spectral disorders in humans.

Following this, Dr Lisa Nicholas (University of South Australia) described her elegant experiments investigating the specific influence of obesity exposure in the peri-conception period. In these studies, sheep embryos were transferred from obese ewes to a control mother; in half of the cases, the obese mother was made to lose weight prior to the transplant. Many of the adverse effects in the offspring, including impaired insulin signalling, were ablated when the mother underwent weight loss. Given that an estimated 93% of pregnant women attempt to lose weight before pregnancy, these results are of considerable relevance. Questions remain regarding whether *in utero* effects are caused by alterations in blood flow, nutrient transfer or the profile of cytokines secreted by the placenta. Evidence for a model of enhanced nutrient transfer in obese mothers was discussed in the Tuesday

afternoon symposium, *Mother, placenta, fetus and lifelong health*. Here, Professor Theresa Powell (University of Texas Health Science Center, San Antonio) described how fatty acid transporters (such as FATP2) and the glucose transporter GLUT1 are expressed more highly in the basal placenta membrane of obese mothers. Maternal obesity also appears to stimulate the mTOR signalling pathway in the placenta, promoting nutrient uptake. In addition, maternal obesity is associated with decreased expression of the protein adiponectin, which is thought to normally inhibit placental nutrient transfer. Professor Powell's studies found that infusions of adiponectin in obese pregnant mice was able to return fetal birth weights to control levels, suggesting a mechanisms by which excess nutrient transfer to the foetus can be restricted.

Alternate day fasting – a celebrity diet that works?

A considerable audience gathered to hear Dr Krista Varady's lecture, *Alternate day fasting: a novel dietary restriction regimen for weight loss in humans*, which described the results of an 8 week pilot study in the USA. This involved placing 20 obese males and females on a regime which limited their dietary intake to 25% of their needs on three days a week. On the remaining days, the participants were free to choose what they ate. In the first 4 week block, the participants were control fed 500 calorie meals on the 'fast days', but in the second half of the trial the subjects prepared these themselves, using dietary advice. Only four participants dropped out of the study and these did so at a fairly early stage. The rest lost an impressive average of 5.6 kg with the rate of weight loss being fairly steady throughout the study period. In conventional restrictive diets (especially those involving no additional exercise) this loss is usually lean muscle, rather than fat, which reduces the amount of metabolically active tissue, making it even harder to lose weight. The key finding for this study however, was that about 90–95 % of the weight loss was fat. The subjects also lost about 4 cm of their waistline, lowered their systolic blood pressure by 6 mmHg and reduced their LDL cholesterol levels by 20–25%. Subject compliance, as assessed through feeding diaries, was 87%. Although one might presume that the participants would 'binge' on the non-fasting days, the subjects were found to only consume 110% of their energy needs and so didn't make up the deficit. Many of them were even happy to carry on the diet with Dr Varady stating that 'after the initial two weeks most have no problem with the fast days'. Some of the audience were sceptical about the long term effects and Dr Varady admitted that the rate of weight loss did seem to drop after 24 weeks. Nevertheless, this approach certainly gives food for thought...

Exercise – we know it's good for you, but how does it work?

Another popular session was the plenary lecture, *Health-promoting effects of exercise in diabetes and obesity: from molecular mechanisms to clinical action*, given by Professor Juleen R. Zierath (Karolinska Institutet, Sweden). Exercise has been established as an effective strategy for weight loss and this talk explored how exactly these beneficial effects are translated. Professor Zierath described how glucose uptake capacity varies across different muscle fibre types and is particularly enhanced in slow-twitch oxidative fibres, due to greater expression of components of insulin-stimulated signalling pathways. When one of these components, calcineurin, is over-expressed in mice fed high-fat diets, insulin-stimulated glucose uptake is increased and the mice are less likely to develop insulin resistance. In a human study where diabetic patients underwent a week-long exercise programme, most improved their glucose tolerance apart from those with the Type 1 condition (characterised by low insulin production). This suggests that exercise acts at the level of improving insulin sensitivity of muscle cells, rather than increasing insulin production through β cell activation. Sensitivity is mediated in part by the availability of the GLUT4 glucose transporter on the plasma membrane; this translocates to the cell surface when the energy sensor AMPK is stimulated. Physical exercise appears to enhance AMPK signalling activity through increased expression of diacyl-glycerol kinase (DGK), an enzyme which converts diacylglycerol to phosphatidic acid. In DGK deficient mice, glucose uptake and lipid oxidation are impaired and the metabolic response to fasting or high fat diets is blunted. These mice also show reduced AMPK activation and are prone to becoming insulin resistant on high fat diets. In humans, Type 2 diabetes can be improved with exercise and this is associated with raised DGK levels. Professor Zierath suggested that treatment strategies should focus on exercise regimes or drugs that promote DGK, and hence AMPK, activity. But how does exercise induce changes in protein expression? Professor Zierath cited studies which found that humans on high fat diets show genome wide changes in DNA methylation that were not easily reversed. In addition, muscle biopsies taken after acute exercise have reduced promoter methylation for genes encoding enzymes involved in the exercise response; this hypomethylation allows more efficient recruitment of the transcription machinery and hence greater protein expression. A further study indicated that hypomethylation is more extensive following 35 minutes of high intensity exercise (80% of VO_2 max) compared with 75 minutes of lower-intensity exertion (40% of VO_2 max). This gives credence to claims that short intense bursts

of exercise can be more beneficial than longer, aerobic workouts. As we understand more about how exercise induces physiological changes, our ability to tailor weight-loss programmes can only improve.

Too much of a good thing – the physiological effects of a hedonic diet

The physiological changes induced by excess calorie consumption were explored in the Wednesday morning symposium, *Peptide modulation of hedonic food intake*. Professor Suzanne Dickson (The Sahlgrenska Academy at the University of Gothenburg, Sweden) introduced the session by outlining the central role of the hormone ghrelin in activating reward pathways. During fasting periods, this is produced by oxyntic glands in the stomach and activates the GHS-R1A receptor in the brain to stimulate increased food intake. The hormone also mediates the reward response by promoting dopamine release into the nucleus accumbens. Directly injecting ghrelin into various areas of the brain stimulates feeding behaviour. Professor Dickson's work, however, has demonstrated that ghrelin mediates its effects through an orchestra of different neurone types, besides the opioid compounds. Curiously, inhibiting different ghrelin-activated pathways can cause differential effects. Suppressing neuropeptide Y (NPY) neurones, for instance, decreases food intake but not food motivation (assessed by how many times a mouse is prepared to pull a lever to obtain a food pellet). Inhibiting the opioid system, meanwhile, reduces food motivation but not overall intake. Reward-response pathways were explored further by Professor Roger Adan (University Medical Centre, Utrecht), who described experiments where ventral tegmental area (VTA) neurones were engineered to fire in response to injections of clozapine. Stimulating these neurones (which release dopamine in the nucleus accumbens) was found to increase food-motivated behaviour in mice. Professor Carlos Dieguez (University of Santiago de Compostela) meanwhile outlined the emerging role of opioids in modulating ghrelin-induced feeding stimulation. Ablating or inhibiting opioid receptors can reduce long term food intake and protect against obesity induced by high-fat diets. Specifically, antagonists against the kappa opioid receptor impair ghrelin-stimulated food intake, with hypothalamic transcription factors normally unregulated by ghrelin (such as *bsx* and *pCREB*) showing reduced expression. This implies that an active opioid pathway is essential to potentiate the feeding-stimulation effects of ghrelin.

Dr Stephanie Fulton (University of Montreal) moved the discussion to leptin, an antagonist of ghrelin which inhibits dopaminergic and GABA neurones in the VTA to induce satiety and suppress food intake after a meal. Ablating leptin receptors in VTA neurones

causes mice to increase food intake, leading to obesity. Dr Fulton described her recent work where Stat3, a downstream effector of leptin signalling, was knocked out in mice to suppress leptin signalling in dopaminergic neurones. The mice were trained to adopt a 'hedonic feeding pattern' where they consumed their daily intake within a 4 hour window. When the mice were given an extra hour of access to high fat food (the so-called 'dessert test'), there was no differential intake between the Stat3 knockouts and control groups, suggesting that food-related reward pathways were unchanged. On the other hand, the Stat3 knockouts showed greater voluntary running behaviour, indicating that the 'euphoria effects' of exercise were enhanced. This indicates that different neurone populations mediate the effects of leptin on reward pathways and that GABA, rather than dopaminergic, neurones may act to suppress food intake.

The role of perivascular fat in the interplay between obesity and cardiovascular health

The mechanisms by which obesity affects cardiovascular health were explored in Tuesday's symposium, *Perivascular fat: Role in metabolic and cardiovascular disease*. Perivascular adipose tissue (PVAT) accumulates around blood vessels and is metabolically active, secreting a range of cytokines, hormones and chemokines – together known as 'adipokines'. Aortas with a covering of PVAT show a reduced constriction response to the vasoconstrictor noradrenaline; this is termed the 'anti-contractile' effect. Professor Anthony Heagerty (University of Manchester) described how the anti-contractile effect is lost in the metabolic syndrome and that this is thought to be due to inflammation of PVAT. In studies where mice were fed a high-fat diet, glucose tolerance was improved in animals that were additionally subjected to tape-worm induced eosinophilia. Eosinophils function to reduce proinflammatory cytokines; in their absence classically activated macrophages promote an inflammatory response which reduces adipokine secretion from PVAT. Additionally, eosinophil loss causes hypertension, suggesting that obesity-associated hypertension may be mediated in part by the protective effect of eosinophils on PVAT. Curiously, anti-contractile activity can be restored in patients who undergo bariatric surgery, which generally improves systolic blood pressure. This opens a door to future work investigating the role of macrophages, eosinophils and other inflammatory cells in mediating the effects of obesity.

The importance of gut microbiota... you are what your microbes eat...

Professor Graham Dockray's (University of Liverpool) well attended keynote lecture,



Gastrointestinal hormones and the dialogue between gut and brain, provided a lively introduction to the myriad components that affect feeding behaviour in response to nutrient status. The second part of his talk, however, focused on how imbalances in the gut microbiome can deregulate this dialogue. Bacterial populations are usually a balance between the bacteroidetes and the firmicutes, yet high-fat diets increase the proportion of the latter. This promotes lipo-polysaccharide production, inducing inflammation and increasing gut permeability. Professor Dockray presented results showing that mice infected with helicobacter showed increased expression of plasminogen activated inhibitor 1 (PAI1), which attenuates satiety signalling pathways. This adds another realm of complexity to the interaction between inflammation, obesity and the hormonal control of feeding behaviour.

Does hypoxia in the womb increase susceptibility to obesity?

The influence of the fetal environment was explored further in the keynote lecture *New insights into the fetal origins of adult cardiometabolic disease*, given by Professor Sandra Davidge (University of Alberta). Her studies have found that placing pregnant mice under hypoxic conditions (17% oxygen) during their third trimester causes the offspring to show a 'prematurely aged cardiovascular system'. These mice showed reduced diastolic filling, left ventricular hypertrophy (males only) and decreased pulmonary tension, yet the phenotype only manifested at 12 months, suggesting it requires a 'second hit' of ageing. At 4 months, the mice were identical to the controls unless challenged with induced myocardial infarction; in this case, the hypoxia-exposed individuals showed considerably impaired recovery. More recently, Professor Davidge has investigated whether perinatal hypoxia increases susceptibility to obesity caused by

a high fat intake. When mice were fed high fat diets, those exposed to perinatal hypoxia exhibited increased intra-abdominal fat, reduced glucose tolerance and greater insulin resistance. Critically, there was no difference in these parameters between hypoxia-exposed and control mice fed normal diets, demonstrating that hypoxia *per se* does not promote obesity, but requires a second challenge to manifest a phenotype. This raises the question of whether drugs that improve placental blood flow (and thus oxygen delivery) can protect against hypoxia-induced obesity susceptibility that may be caused by pregnancy complications. In hypoxia-exposed mice fed high fat diets, treatment with the vasodilator resveratrol improved many aspects of metabolic syndrome, suggesting that this could be an effective preventative measure in humans.

Another reason to avoid stress...

Perinatal influences were also discussed in the session *Peptide modulation of hedonic food intake*. Here Dr John Menzies (University of Edinburgh) described how subjecting rats to stress increases their preference for palatable food. To see if this can be translated gestationally, pregnant mothers were subjected to 'social defeat' scenarios over an extended period. The offspring showed enhanced stress responses with increased plasma corticosterone levels, besides a greater motivation towards palatable food. Curiously, a potential mechanism was proposed in the Wednesday Research Symposium *Gastrointestinal flexibility: Ecology, evolution and microbial symbiosis*. In this session, Dr Gaelle Boudry (INRA, France) described how exposing neonatal rat pups to stress caused an increase in early gut permeability and increased inflammation in adult life. As chronic inflammation is associated with leptin and insulin resistance, it is pertinent to ask if our high-stress modern lifestyles are contributing to the obesity epidemic.



2014 *Forthcoming events*

10–12 Sept

Obesity: A Physiological
Perspective
Newcastle Upon Tyne, UK
www.physoc.org/topicobesity

19 Sept

H³ symposium:
Public engagement as a
'Pathway to Impact'
Hodgkin Huxley House,
London, UK
[www.physoc.org/
publicengagementh3](http://www.physoc.org/publicengagementh3)

28 Nov

H³ symposium:
Microvascular physiology:
Implications for understanding
intravenous fluid therapy
Hodgkin Huxley House,
London, UK
[www.physoc.org/
h3symposiumnov2014](http://www.physoc.org/h3symposiumnov2014)

2015

10–12 Apr

Ageing and Degeneration: A
Physiological Perspective
Royal College of Physicians,
Edinburgh, UK
www.physoc.org/ageingtopic



Delegates outside the QEII Conference Centre

Meeting Notes

Physiology 2014

30 June – 2 July 2014,
The QEII Conference Centre
London, UK

Over 1,000 physiologists attended The Society's main annual conference held this year in the purpose-built Queen Elizabeth II Conference Centre in Westminster. The location came in especially handy for the successful launch of Engaging with Parliamentarians at the House of Commons on Monday 30 June.

The programme for Physiology 2014 included some 25 symposia, including the inaugural Presidential Symposium, and five prize lectures. Attendees also enjoyed the poster sessions of over 500 communications, 80 oral communications and two

demonstrations. There was also the Welcome Reception at Central Hall Westminster on Monday 30 June, with entertainment from GI Distress, and the Society Dinner, which took place on Tuesday 1 July.

Physiology 2015 takes place on 6–8 July 2015 at the Motorpoint Arena, Cardiff and registration opens on 1 January – we hope to see you there!

.....

Rachel Harper

Marketing Specialist – Europe,
ADInstruments, UK
Major Sponsor

The Physiological Society’s ‘Physiology’ conference is the most important conference in the ADInstruments European office’s calendar as it allows us to meet with our core audience and current customers, gaining important feedback and also allowing us to keep researchers and educators up to date with our innovative product offering.

We were pleased to welcome a wide selection of visitors to the booth, with some taking part in our fun interactive demonstration, which proved popular with delegates. The activities at the outreach tent were great at gaining the attention of the public and even allowed ADInstruments staff to take part in some fun networking with The Physiological Society staff while bouncing on the space hoppers.

We look forward to building our relationship with The Society over the coming years and events.

.....

Christopher Torrens

University of Southampton, UK
Ordinary Member

Physiology 2014 was a packed three days of physiology and much, much more.

Monday: Discussing the value of teaching in higher education before judging posters in the Science of Life competition; the projects and the quality of the presentations were superb. After that it was off to the oral presentations to see what was new and to lend some moral support to colleagues.

Tuesday: Starts with an excellent breakfast and conversation with the editors of *Physiological Reports*. Next it was down to the Outreach Tent to compete with Westminster Abbey and the local sites to bring physiology to the public. From there judging posters for the Rob Clarke Awards and

again so impressed by the quality of both posters and presentation – considerably better than some of my own PhD efforts. A quick spell on the Membership desk espousing the benefits of membership before the days ends with Prof Winston’s plenary and dinner with colleagues, old and new.

Wednesday: Symposia in the morning followed by Prof Sleight’s excellent Paton Lecture. Next off to the Society Reps meeting and had some interesting discussions. Finally take in another symposium before making sure my student is ready for her poster session (she was and did an excellent job). All done, bring on Physiology 2015...

.....

James Kerin

Marketing Director, Cairn Research
Exhibitor

The main Physiological Society meeting is a key date on our calendar. In fact, we have been attending these meetings for more years than we care to remember, and we shall of course continue to support them as we continue to grow. In addition to exhibiting our latest offerings, it is a great opportunity to see old friends and meet new ones.

Fortunately for us there is a high proportion of expert (present and potentially future) customers who are particularly helpful in the identification and development of new products. Our new four-way image splitter, on display for the first time, is an excellent example of this.

We would like to thank The Physiological Society for looking after us each year and making us feel welcome to all elements of the meetings, including all the social events too!

We shall of course be in attendance in Cardiff next year and look forward to seeing everyone there.

.....

Robert Banks

University of Durham, UK
Ordinary Member (Retired)

The Main Meeting of The Society always promises excellent science in good company, and Physiology 2014, meeting in its new home city, certainly lived up to expectations.

The packed programme meant that one had to be highly selective. This was especially true in the poster sessions, where, as usual, there seemed to be too little time and space available.

The scientific highlight for me was probably right at the start with the Presidential Symposium on emerging technologies for physiology and neuroscience, but all the symposia I attended were unfailingly interesting and of a high standard.

I also had a role to perform as a judge for the Rob Clarke awards. Meeting a group of young physiologists at the very beginning of their careers is always a pleasure. Socially, too, the meeting was a great success. With the exception of the poster hall, the venue was roomy and comfortable; and where else could you have a view like this from the gents’ toilet? And if you missed the dinner you missed a real treat; not only fine food, but a magnificent display of synchronised serving!



The view from the gents’...

.....

Bijal Patel

King’s College London, UK
Affiliate Member

As an early career physiologist it was a real pleasure to be involved in organising the Early Career Physiologists Symposium at King’s College London.

I think it is important to be involved in such events as it gives you the opportunity to interact with scientists from all over the world in an informal environment. Moreover, you may bump into the same people at the main meeting, and it’s nice to see a friendly face amongst the sea of scientists at the conference venue.

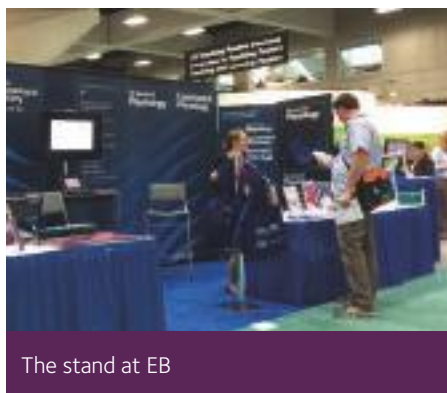
The highlight of Physiology 2014 for me would have to be the public lecture given by Sir Robert Winston. He managed to captivate the entire audience with his lecture which was very insightful, and one of the best talks I personally have ever attended.

Experimental Biology 2014

26–30 April 2014,
San Diego, USA

Nick Boross-Toby

Director of Marketing,
The Physiological Society



The stand at EB

Our regular attendance at EB as a formal guest society of the American Physiological Society (APS) continued in 2014 when we returned to sunny San Diego to promote The Society and its journals. Our partnership with the APS has flourished over the last few

years, not least illustrated by the new OA journal, *Physiological Reports*, which has had such a successful start in its first year.

Philip Wright, Mike Shipston (then Chairman of Publications Committee), David Wyllie (then Meetings Secretary) and I met with the APS Council to give an overview of The Society's 2014–18 Forward Plan. This engendered much discussion and further areas of collaboration are being identified, including establishing a joint Data Working Group to support the activities of our journals.

David Wyllie and I also presented a formal proposal to make Physiology 2016 a joint endeavour with APS in Dublin. There was great enthusiasm and support for the proposal so stay tuned for further details over the coming weeks.

Our stand in the exhibiting hall was as busy as ever with over 500 visitors. The Society also sponsored two symposia during the meeting. Professor Carel le Roux organised the first, reviews of which will be published in *Experimental Physiology*, on *Physiological and pathophysiological signalling between the gut and the kidney: role in diabetic kidney disease*. The Journal of Physiology will be publishing reviews of the second, jointly organised by Professors David Paterson and Julian Paton and entitled *Insights gleaned from pharmaco-genetic dissection and modelling of cardio-respiratory neural networks*.

All three journals held constructive meetings of their editorial teams, chaired by the respective Editors-in-Chief. Simon Rallison,

Director of Publications, took the opportunity of comparing notes with the other societies and publishers exhibiting journals at the conference; an informal but useful exercise in benchmarking journal performance and picking up new ideas.

We bid a fond farewell to Professor Ron Lynch (University of Arizona), Chair of the APS Joint Programme Committee (JPC) and welcomed the new Chair, Professor Robert Hester (University of Mississippi). The JPC is responsible for developing and ensuring the scientific integrity of the APS's EB programme, no small feat given the size and complexity of this meeting.

This year also saw the end of Professor Kim Barrett's (UCSD) tenure as APS President and the beginning of the Presidency of Professor David Pollock (University of Alabama at Birmingham). The Society would like to thank Kim for her continued support of our partnership and we look forward to continued collaborations with the APS under the leadership of the new President. We also congratulate APS President-Elect, Patricia E. Molina (Louisiana St University Health Sciences Center).

Finally, your Director of Marketing made his rock-star debut singing with GI Distress and the Fabulous FASEBettes. If you missed it in 2014, worry not, he will be back next year when EB returns to Boston at the earlier slot of 28 March to 1 April. Society Members benefit from APS Member rates when they register, as we are a designated 'guest society'. Hope to see you there!

The GL Brown Lecture 2014

David Eisner

University of Manchester, UK

As a long-time member of the Society who has enjoyed many previous GL Brown Lectures, I was delighted to be asked to give this year's. My 'tour' was made up of nine venues. It certainly exposed the deficiencies in my knowledge of geography; how could it possibly take so long to travel from Southampton to Cambridge and why could I not get a direct train from Bristol to Milton Keynes? I travelled a total distance of almost

3000 miles. The various rail companies behaved more or less impeccably. My PhD students suggested that I should have had a T-shirt made listing the venues and, indeed, gave the impression that they would have happily joined me as roadies. A particular delight was to catch up with old friends and make new ones. It is impossible to list all the highlights or, indeed, to thank all my hosts who contributed to making it such an enjoyable time. I will, however, long remember the oldest member of any of my audiences, Otto Hutter, pointing out that he was GL Brown's PhD student and that, since he supervised my PhD supervisor (Denis Noble), there was a direct genealogical connection linking me to GL Brown. My lecture at the Open University was apparently the first time that a GL Brown Lecture had been delivered there. It was timetabled to coincide with a Science Fair and the enthusiasm of the school students for science was tangible. I gave a different lecture to these students but felt that it still fitted within the aim of the GL



David Eisner with Prof Otto Hutter (a PhD student of GL Brown). Photo courtesy of Dave Miller

Brown Lecture to 'stimulate an interest in physiology' in a 'younger audience'.

David Eisner gave the 2014 GL Brown Lecture at Queens University Belfast, Bristol, Cambridge, Edinburgh, Glasgow, Liverpool, The Open and Southampton Universities and Imperial College, London

Appetite control and exercise: not just energy-in and energy-out

‘the differences between the intakes of food must originate in the differences in energy expenditure’ (Edholm *et al.*, 1955).

John Blundell

Chair of PsychoBiology,
University of Leeds, UK

‘the late Henry Taylor favoured a model that linked energy intake to expenditure in a J shaped curve (personal communication, late 1970s). The first part of his concept was that energy intake was in exact homeostasis with energy expenditure under conditions of high energy expenditure. The second part was that there is a failure of homeostasis in sedentary lifestyles because of its accompanying low energy expenditure. He postulated that bodily signals go awry in sedentary lifestyles; when a person does no physical work, the body will not recognize that it is being overfed. Sedentary persons may lose the innate ability to compensate for inactivity by reducing their eating.’

Cited by Jacobs (2006), p1234.

Ideas proposed over 50 years ago but left neglected until recently are defining a revitalised perspective of energy balance (EB) in relation to body weight, and the contribution of behaviour to the physiology of energy balance. Edholm and co-worl (1955, 1977) sought to establish a fundamental relationship between energy expenditure (EE) and energy intake (EI). Behind this was ‘*the desire to find out more about the mechanisms which relate intake to expenditure – what regulates appetite, in fact*’ (Edholm *et al.*, 1955, p286). Edholm’s views implied an impact of physiology on behaviour and an influence of energy expenditure on appetite control. Strangely this view was ignored and the general approach to the issue was largely abandoned. However, just because Edholm’s views have been overlooked does not mean that they were wrong.

The neglect of Edholm’s views left a void which was filled by a simple mechanical approach to energy balance and body weight. This is reflected in the common depiction of energy balance as a set of kitchen scales with food on one pan and physical activity on the other; whichever has the highest value determines whether there will be a positive or negative energy balance. This model is false and gives a misleading impression of how the system works. The EB approach to appetite control and obesity is not just a case of energy-in and energy-out. The kitchen scale model represents a static view of EB and has provided a widely used rule of thumb that a change in EB of 8000 kcal will lead to a 1 kg change in body weight. This rule is false and leads to wildly optimistic expectations of weight change. Using a dynamic model of energy balance (Hall *et al.*, 2011; Thomas *et al.*, 2013) gives recognition to a physiological regulated system that actively readjusts behaviour in response to challenges, and leads to more realistic computed changes in body weight.

A regulated physiological system resonates with demonstrations that alterations in physical activity influence appetite control, and that changes in food consumption (diet) adjust behavioural activity (Stubbs *et al.*, 2004). Changes in NEAT (non-exercise activity thermogenesis) illustrate how the effects of mandatory overconsumption are offset by increases in spontaneous activity (Levine *et al.*, 1999). Conversely, obese people given supervised and measured sessions of physical activity (five 1 hour sessions per week for 12 weeks) show clear changes in appetite control; these include an increase in fasting (early morning) hunger and an improvement in the strength of post-meal satiety signalling (King *et al.*, 2009). Together these adjustments influence the overall EI in response to the imposed EE and partly determine the observed changes in body composition. An important feature of these types of manipulations is the very large individual variability in the response to a challenge. People do not all respond in the same way to overconsumption or to imposed

‘People do not all respond in the same way to overconsumption or to imposed exercise’

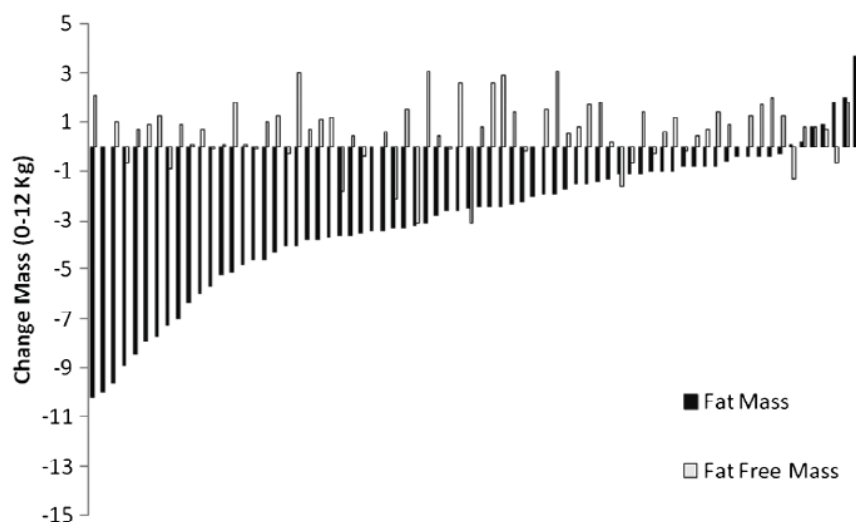


Figure 1. Changes in body composition in a group of female obese participants ($n = 30$) who have undertaken a 12 week period of mandatory physical activity (5 sessions per week). Diet was not controlled and participants were free to eat whatever they wanted. (Caudwell *et al.*, 2013)

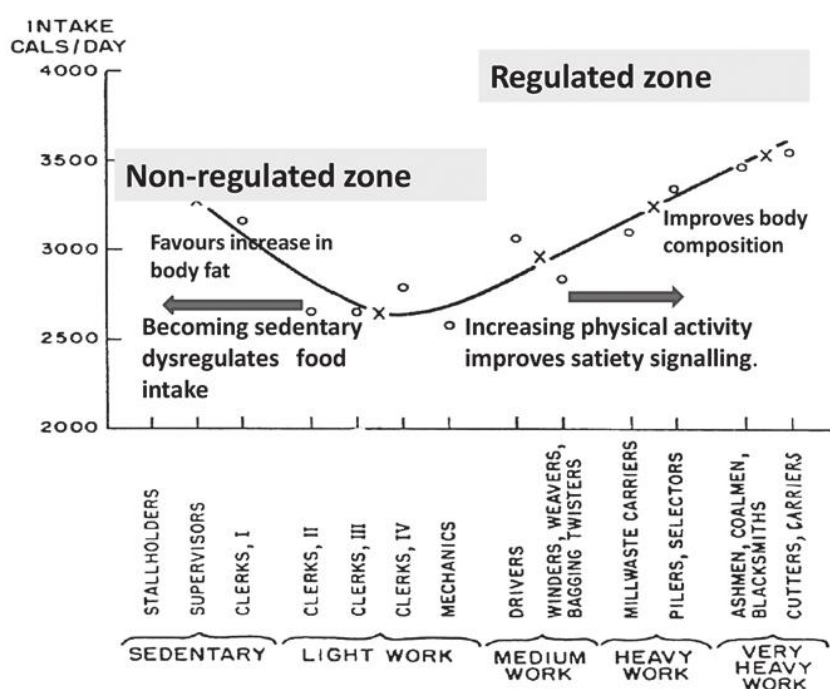


Figure 2. This figure show the diagram taken from the work of Mayer *et al.* (1956) on food intake in relation to physical work by workers in the Bengal jute mills. The figure has been interpreted to include outcomes from recent studies on physical activity and objectively measured food intake. The diagram has been modified after Mayer *et al.* (1956) and Blundell (2011).

exercise. The average response of a group of people is not very informative. For example when exercise sessions are monitored to eliminate the possibility of non-compliance (usually a big factor in exercise studies), about 15–25% of participants gain weight (Fig. 1).

Importantly fat mass is significantly reduced along with waist circumference (King *et al.*, 2008; Caudwell *et al.*, 2013) and any weight gain is usually (but not invariably) almost entirely fat-free mass (FFM). This action of exercise on body composition is one reason to

expect that the adaptive response to physical activity energy expenditure involves both metabolism (resting metabolic rate) and behaviour (food intake) (Hopkins *et al.*, 2014). This again illustrates why a simple rule of calories to weight change is not plausible.

Interestingly, this wide variability in body weight (and body composition) in response to exercise stimulates thinking about the link between energy expenditure and appetite (as Edholm suggested). First, as noted by the late Henry Taylor (see box), the control over appetite (food consumption) depends upon the level of energy expenditure. As reported above, making people active increases the strength of satiety signalling. Other studies have shown that sedentariness (reflected in low leisure time physical activity) is associated with weak satiety (especially to fat) and to the trait of disinhibition, which is a marker for susceptibility to overeating (Blundell *et al.*, 2005). Together these findings map onto the picture of calorie intake and physical work proposed by Jean Mayer (a contemporary of Edholm). The inverted-U function (Fig. 2) reported a paradoxical increase in calorie intake at low levels of energy expenditure (Mayer *et al.*, 1956). A recent interpretation of this figure has identified 'regulated' and a 'non-regulated' zones of appetite control corresponding to

the background level of physical activity EE (Blundell, 2011).

Secondly, these studies draw attention to distinct effects on appetite arising from different components of the energy budget. The observation that the size of meals and daily EI are both associated with the amount of FFM and not with fat mass (FM) or BMI, draws attention to the role of body composition in determining food intake (Blundell *et al.*, 2011). In turn the fact that the variance in resting metabolic rate (RMR) is determined largely by FFM (about 60%) whereas FM only contributes about 7%, suggests that RMR could be a driver of the motivation to eat and of EI (Caudwell *et al.*, 2013). This formulation indicates that the 'adipocentric' concept of food intake control is incomplete and should be amended to include a role for the action of fat-free mass (Blundell *et al.*, 2012). How should these findings be interpreted? To describe the operations in rather crude terms, the energy expenditure from RMR applies a uniform and tonic pressure on appetite whereas the energy expenditure from physical activity is more complex and unpredictable (at the level of the person) and depends on changes in body composition, gastrointestinal peptides and individual variability in biological responsiveness. Energy balance is not just a case on energy-in and energy-out.

Over the next decade there are great opportunities for research to examine in more detail the mechanisms through which physical activity improves satiety signalling, and the physiological processes through which sedentariness undermines the homeostatic regulation of appetite.

Acknowledgements

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Body fat: our own Janus

Despite its negative reputation, body fat or adipose tissue is – in the right proportion and quantity – fundamental to many physiological functions. Too much body fat, however, is strongly associated with diseases such as Type II diabetes, cardiovascular diseases and some forms of cancer. Body fat is more than just a passive tissue and an improved understanding of its properties will enable us to better target obesity.

*E Louise Thomas
& Jimmy Bell*

Metabolic and Molecular Imaging
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London, UK

‘a media driven vision of the ‘ideal body’ having little or no body-fat, is distorting the true place of adipose tissue in human physiology and its importance to human health’

With the discovery of leptin, adipose tissue (commonly referred to as ‘body-fat’) was transformed from a humble tissue to a complex and intricate organ. Today we know that adipose tissue interacts with virtually every organ in the body to ensure optimal homeostasis. Yet, most people continue to view adipose tissue in a negative light, ignoring its pivotal role in maintaining our health. But the story of adipose tissue is not as straightforward as we initially thought; it turns out that it is not only about how much fat we carry but also about its composition and distribution.

Obesity is endemic in many parts of the world, with little signs of abating. If obesity continues to increase at the current rate, it is estimated that well over 1 billion people in the world will be overweight or obese by 2050. This, together with a media driven vision of the ‘ideal body’ having little or no body-fat, is distorting the true place of adipose tissue in human physiology and its importance to human health. This negative view is best exemplified by a survey of young girls whose number one ‘magic wish’ was be thin (Kilbourne, 1994). Clearly, a re-balancing of our attitude to fat is urgently required. It is essential that we have a better understanding of the different functions of adipose tissue and how content and distribution can affect our health. It is essential to dispel the current dogma that all body-fat is bad and undesirable; at the same time we need to become more aware of the physiological cost of carrying too much body-fat and the health implications of depositing it in the ‘wrong’ places.

The anatomy of adipose tissue

Adipose tissue (AT) is a beautiful and complex organ fundamental for the optimal functioning of our bodies, affecting virtually

all organs and cell types, mainly through the production of chemical signals known as adipokines. Adipose tissue is associated with many fundamental physiological functions, including fertility and immune responses, affording us protection from the environment, as well as modulation of our moods and appetite. Adipose tissue can be found in almost every part of our anatomy making it the largest organ in our body, from the large subcutaneous depots covering our bodies (especially around the waist and hips), to distinct depots behind our eyes, around our heart and behind the knees (Fig. 1).

In the general adult population, levels of adipose tissue ranges from 3.5 to 98.0 kg, corresponding to a percentage body-fat of 4.0–68.0%. So what is the right amount of AT for an adult? At present we do not have exact values for this, but, in terms of a healthy percentage body-fat, it is recommended that women aim for 21–24%, while men should aim for 14–17% (Jeukendrup & Gleeson, 2010). Similarly, it is suggested that the percentage body-fat for women should not go below 10–13% or 2–5% for men, referred to as essential fat percentage; extremely low levels of AT are known to be associated with metabolic

contraindications, as well as affecting fertility and immune responses to injury and infection. Moreover, let us not forget that individuals with lipodystrophy (a genetic condition where AT levels are extremely low or virtually absent) suffer from many of the metabolic conditions observed in obesity (Capeau *et al.*, 2010).

At a cellular level adipose tissue can be broadly defined as being composed of adipocytes, endothelial and nerve cells (innervation), as well as inflammatory cells including macrophages, neutrophils and lymphocytes. Adipocytes, which are the principal component of adipose tissue, can in turn be subdivided into 'white' (responsible lipid storage and production of most adipokines), 'brown' (associated with thermogenesis – its presence in adults only recently being confirmed) and 'beige' (a sort of half-way house between the first two, but with quite distinct properties) (Park *et al.*, 2014).

Indeed the concept of 'beige fat' has recently attracted much attention given its potential as an anti-obesity mechanism. It turns out that a number of physiological events, including exercise, as well as some natural and pharmacological compounds can increase the thermogenic properties of subcutaneous adipose tissue through a process that has come to be known as 'browning' (Bartelt & Heeren, 2014). It is currently unclear if the process of browning takes place by increasing expression of thermogenic-UCP1 in white adipocyte or by the recruitment of dormant 'beige adipocytes'. Regardless, the overall effect is an increase in whole-body energy expenditure and a reduction in weight and adipose tissue, along with an improvement in glucose homeostasis.

Levels of other cells are highly dependent on the 'health' status of the individual, with for example inflammatory cells increasing significantly in number with obesity, making up to 50% of cells in some adipose tissue depots. These cells are crucial in the chronic and low-grade state of inflammation normally associated with increased adiposity, especially abdominally obesity.

Adipose tissue content and distribution: implications for health and well-being

It is now generally accepted that increased body adiposity can lead to a plethora of metabolic complications including the metabolic syndrome, insulin resistance, type II diabetes, cardiovascular disease and some forms of cancer. At population level the relative risk of developing these disorders appears to increase linearly with increases in AT content. Although most of these studies were based on the use of body mass index (BMI) as a measure of adiposity, the advent

of non-invasive imaging techniques, especially magnetic resonance imaging (MRI), have confirmed some of these findings. Moreover, the capability to directly determine total and regional content has shown that adipose tissue distribution is also important.

We now know for example that 'abdominal obesity' (adipose tissue around the abdomen, both subcutaneous and intra-abdominal – also known as 'visceral fat') does not carry the same risk as 'peripheral adiposity' (adipose tissue around hips and thighs). If anything, the latter is seen as benign and even cardioprotective, especially gluteal-femoral adipose tissue. On the other hand deposition of visceral adipose tissue is strongly associated with the metabolic syndrome, insulin resistance and type II diabetes. So it is not only the quantity but also the distribution of adipose tissue that determines the relative risk observed with increased adiposity.

Ectopic fat

Beside fat accumulation in adipose tissue, lipids in the form of triglycerides can also be deposited in the liver (intra-hepatocellular lipid, IHCL), muscle (intramyocellular lipid IMCL), pancreas (intra-pancreatic cellular lipid, IPCL) and heart. These fat depots are part of what is known as 'ectopic fat', some of which appear to be independent risk factors for the development of type II diabetes (Fig. 2) (Thomas & Bell, 2006). Indeed, an extensive number of published studies have shown that IHCL is an independent risk factor for insulin resistance, while IPCL appears to play an important role in the process of pancreatic dysfunction through 'lipotoxicity'. Elevation of ectopic fat in liver and pancreas is closely associated with central obesity and although the exact mechanism is not fully understood, it may in part arise from the inability of adipose tissue in some individuals to efficiently sequester circulating plasma triglycerides and free fatty acids.

Today, like obesity, the number of individuals presenting elevated IHCL is reaching epidemic proportions, with reports from the UK and USA putting the number of cases in the general population to over 45% (Szczepaniak *et al.*, 2005). The concern over elevated IHCL goes beyond its direct effect on insulin sensitivity, since we know that fatty-liver can eventually progress into liver fibrosis and liver cancer (hepatocellular carcinomas – HCCs) (Powell *et al.*, 1990).

Adipose tissue distribution: MHO, MONW and TOFIs

Over a decade ago Prentice and Jebb wrote a seminal review entitled 'Beyond body mass index', in which they summarised some of the

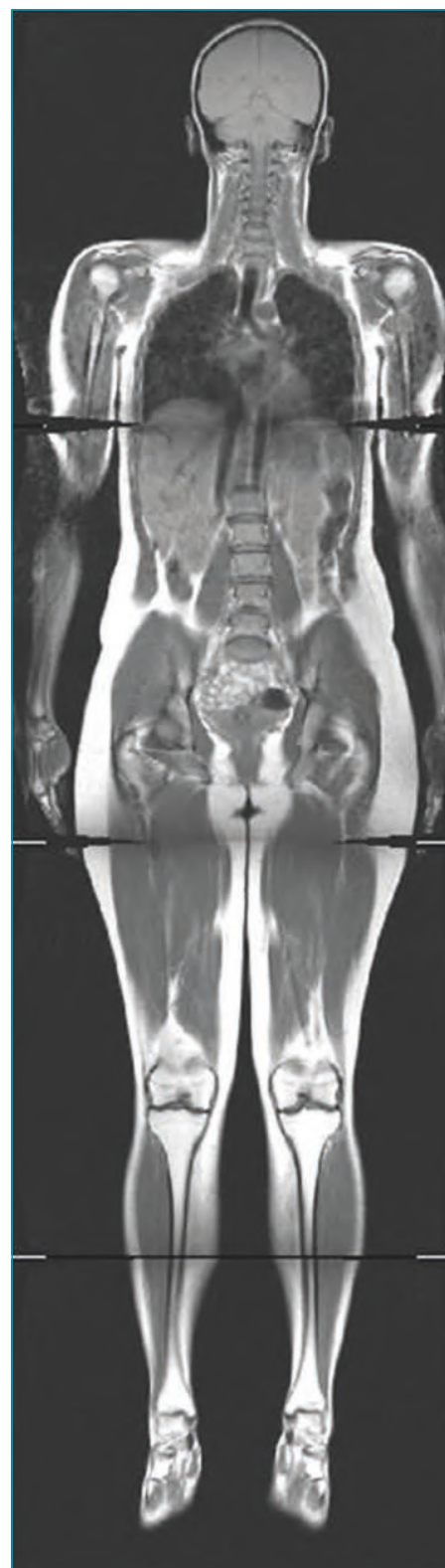


Figure 1. Coronal MR image from a healthy female volunteer, adipose tissue (and bone marrow) appears as bright white in this image and can be seen both covering the outside of the body (subcutaneous adipose tissue) as well as within the body (internal adipose tissue).

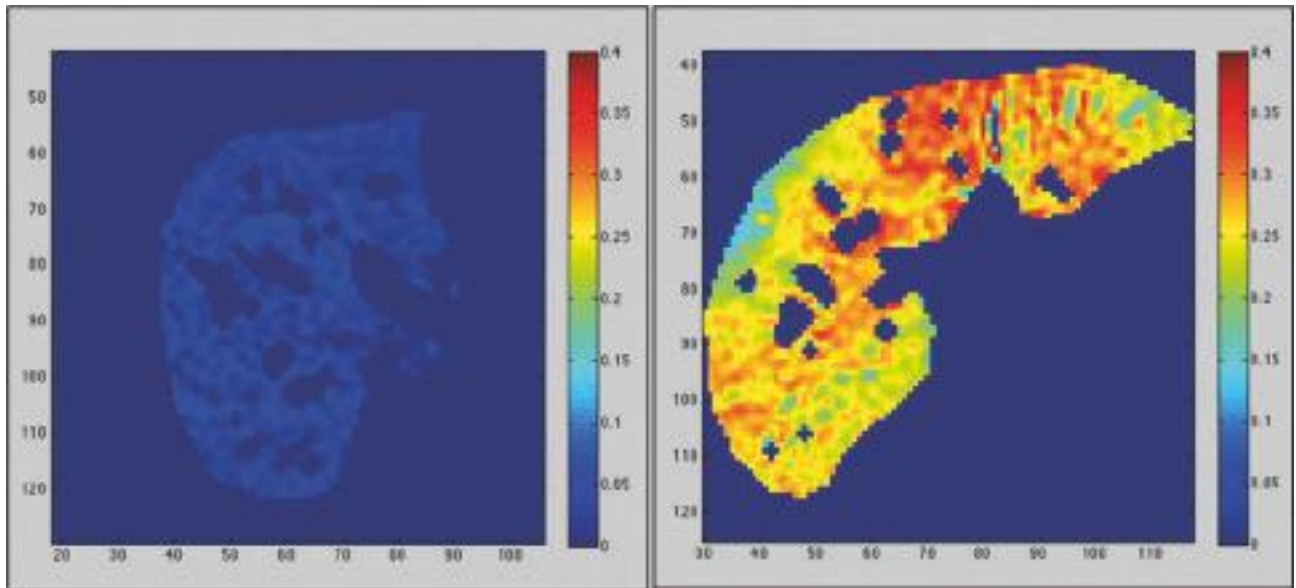


Figure 2. ME heat map from subjects with low IHCL (2.9%) and high IHCL (26.1%) content. Increasing IHCL content is shown by the colour map changing from blue (low) to red (high).

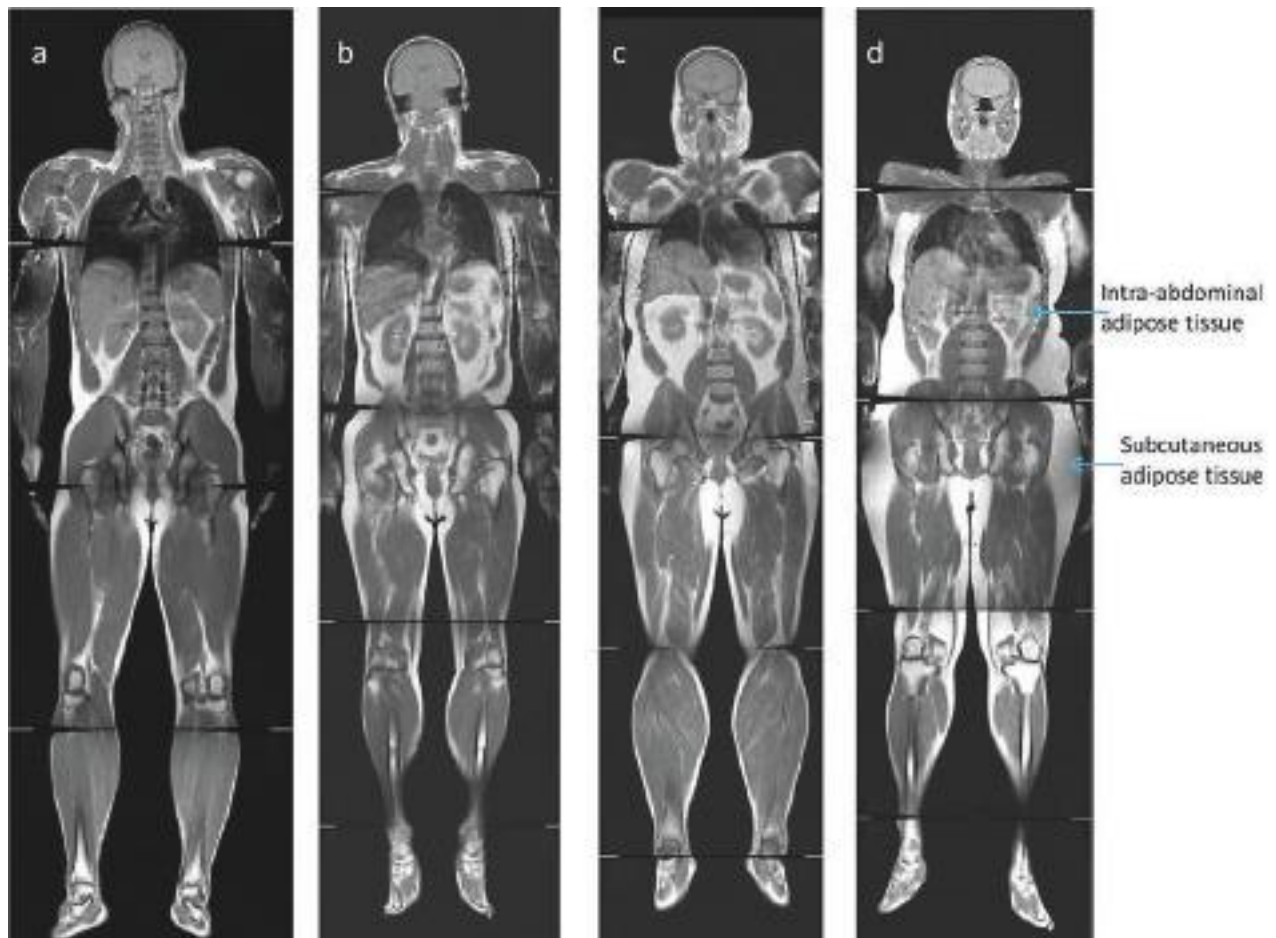


Figure 3. Coronal MRI images from four male subjects, classified from their adipose tissue distribution as (a) lean control BMI 25.5 kg/m², IAAT = 1.0 litres; (b) TOFI BMI 25.8 kg/m², IAAT = 4.6 litres; (c) obese control BMI 36.9 kg/m², IAAT = 5.6 litres; (d) MHO BMI 36.4 kg/m², IAAT = 0.9 litres.

shortcomings of what was seen at the time as the main tool for assessing body adiposity, principally BMI (Prentice & Jebb, 2001). Central to their argument, and those of others, was that the BMI of a subject said little about the actual body composition of that individual, even less about the distribution of adipose tissue. Put simply, a body-builder and a morbidly obese person would be categorised as having the same BMI, despite the fact that the levels of skeletal muscle and adipose tissue are completely different. Indeed, just recently the story of a sportswoman who was told by an NHS nurse to go on a strict diet purely based on her high BMI hit the headlines (Metro, 2014). This is an all too common happening for many athletes with a high degree of musculature.

Similarly, subjects with a similar BMI and overall level of adiposity, but a totally different adipose tissue distribution are usually assumed to have the same risk of disease. However, as we now well know, differences in adipose tissue distribution convey a very different risk of metabolic disease. Differences in adipose tissue distribution arising from sex are a good example of this, where men present more abdominal adiposity than women and consequently carry a higher risk of metabolic disease. Similarly when women go through the menopause, despite minor changes in body weight, significant changes in adipose tissue distribution are observed, reflecting increasing risk of metabolic disease.

Since then, and with the introduction of MRI and CT in clinical studies, the importance of accurately determining adipose tissue distribution has become abundantly clear. Subjects matched for BMI and waist-to-hip ratio can have significantly different levels of visceral adipose tissue and ectopic fat (Thomas *et al.*, 2012). These differences were crucial in unravelling the metabolic and physiological differences observed between subjects with identical anthropometric parameters. In turn this led to the identification of a number of subphenotypes, including the 'metabolically healthy obese' (MHO), the 'metabolically obese but normal-weight' (MONW) and the 'TOFI' (thin-outside-fat-inside) individuals (Fig. 3). Each of these sub-phenotypes represents significant variations in adipose tissue distribution and relative risk of developing insulin resistance or type-2 diabetes. Thus, it is no longer possible to define subjects simply based on BMI or other anthropometric dimensions; accurate assessment of adipose tissue distribution has become essential for human studies of obesity and associated risk factors.

Metabolically healthy obese (MHO or 'fat-fit') subjects have been reported by a number of groups and refer to individuals

with increased BMI (and in some cases waist-hip ratio), carrying considerable levels of adipose tissue while still maintaining normal insulin sensitivity, blood pressure, high HDL and low levels of plasma triglycerides (Wildman *et al.*, 2008). The best example of this subphenotype is of course Sumo wrestlers, many of whom have BMI well above 40 kg/m². There are those of course that dispute the existence of true MHO subjects, as they consider any form of obesity as being 'unhealthy', pointing out that all MHO individuals do present with some metabolic abnormalities, especially those associated with inflammatory markers.

Another important subphenotype, the 'metabolically obese but normal-weight' (MONW), comprises lean subjects (BMI <25 kg/m²) with metabolic profiles normally observed in the obese, including reduced insulin sensitivity, reduced HDL and raised blood pressure (Ruderman *et al.*, 1981). With the advent of MRI this subphenotype has been further refined, known as 'TOFI' (thin-outside-fat-inside), showing that central to its dysfunctional metabolic profile is a disproportionate deposition of visceral adipose tissue (Fig. 3), in some cases accompanied by elevated IHCL (Thomas *et al.*, 2012). This subphenotype can be found in a significant proportion of the lean population (>10%), especially amongst those that aim to maintain a 'normal weight' through diet-based lifestyle choices, with little or no physical activity.

Life-style choices for a healthy adipose tissue

The importance of adipose tissue to our health cannot be over-stated. Adipose tissue should not be seen as the passive tissue whose sole purpose was to store excess energy in the form of fat. Adipose tissue is a complex organ with a crucial role in maintaining whole body homeostasis. Moreover, it is no longer about how much adipose tissue we carry, but also its distribution. The lifestyle choices we make will impact on adipose tissue distribution as well as content, so we need to ensure that both a healthy diet and a significant amount of physical activity are part of everyday life. We need to focus more on fitness rather than thinness. Be nice to your adipose tissue and your adipose tissue will be nice to you.

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Food fight: new approaches to preventing and treating obesity

Obesity is a major global public health problem. An improved understanding of the systems regulating body weight is driving the development of novel approaches to regulating body weight.

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‘In England, more than
60% of adults are
overweight or obese’

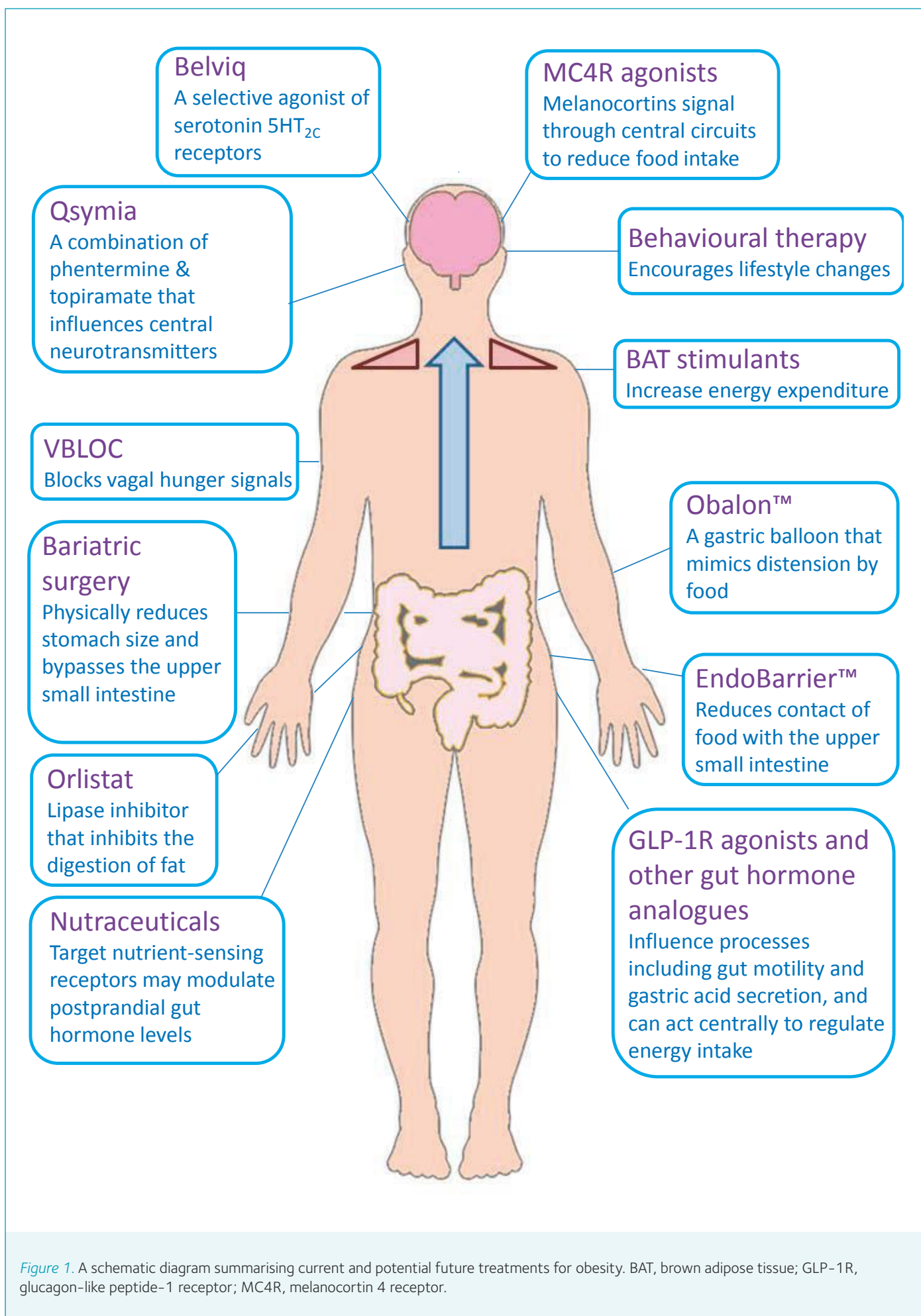
The regulation of body weight should be simple. Balancing energy intake with energy expenditure will result in a stable body weight. If body weight is too high, then all that is required is to reduce food intake and/or increase energy expenditure. And yet the majority of the UK population is overweight or obese, and the costs of treating the obese may, it has been proposed, bankrupt the National Health Service.

The regulation of appetite – of feelings of hunger and satiety – are governed by a complex combination of signalling systems, both in the brain and in the periphery, that have evolved to prevent starvation. It is thought that our ancestors had sporadic access to food, and that in response the human body evolved to store excess caloric intake as adipose tissue for use during times of limited food availability (Ulijaszek, 2002). However, in the modern Western world, food is cheap and plentiful and packed with energy, and developments in transport, entertainment and the work environment mean that more physically demanding energy-expenditure activities are no longer a fundamental part of everyday life. These factors together contribute to the current obesity pandemic. Obesity, defined as a body mass index (BMI) of 30 kg/m² or higher, is now a condition which affects over 500 million adults worldwide (World Health Organisation, 2013).

Obesity is a damaging state. It is associated with increased risk of developing numerous comorbidities, including cardiovascular disease, type II diabetes mellitus, osteoarthritis, stroke and certain cancers, as well as with other factors that reduce quality of life, including underachievement at school, low self-esteem, and mental health disorders (World Health Organisation, 2013). In

England, more than 60% of adults are overweight or obese, meaning that what was once considered a ‘normal’ healthy bodyweight is now no longer normal. Related health problems are costing the NHS over £5 billion a year, and the economy shoulders further, less easily calculated costs due to the associated sick leave and reductions in productivity (Public Health England, 2010).

Central to the problem of obesity is the relative ineffectiveness of most treatments. Calorie-controlled diet and exercise routines work well when adhered to, but compliance rates are low, and public health campaigns are generally unsuccessful. The systems regulating energy homeostasis appear very sensitive in response to energy deficits, but much less responsive to energy excess, and the reward and decision making circuitry of the brain’s mesocorticolimbic system predisposes us to weight gain in our ‘obesogenic’ environment. There is thus a need for other methods of weight control. Current treatment options include very limited pharmacological tools, and bariatric surgery, which produces sustained weight loss and health benefits, including improvements in glucose homeostasis in type II diabetics. Bariatric surgery is becoming more common in the UK and, having previously been reserved for use in the morbidly obese (BMI <40 kg/m²), newly proposed guidelines from



'It may be that a tailored programme of behavioural therapies, nutritional advice, functional foods and combination drug treatments is required to result in effective and sustained weight loss'

.....

the National Institute for Health and Care Excellence suggest considering it for all obese patients with type II diabetes. However, this proposal has significant resource implications and it appears impractical to perform surgery on the large numbers who might qualify. For those who need to lose weight but are unable or unwilling to have surgery, pharmacological therapy may be appropriate. Currently, there is only one prescription weight-loss medication available in the UK. Orlistat is a gastric and pancreatic lipase inhibitor that inhibits the digestion, and thus the absorption, of dietary fat. However, with less than 30% of patients achieving a weight-loss of 5% of their total body weight in 1 year, Orlistat is only modestly effective, highlighting the need for novel drugs or other approaches to address the growing incidence of obesity (Powell *et al.*, 2011).

The central regulation of energy homeostasis involves a number of brain regions, including the hypothalamus, the brain stem, and the aforementioned mesocorticolimbic system. Research over the last two decades has greatly increased our understanding of the circuits controlling food intake, energy expenditure and body weight. Pharmacological manipulation of these circuits may facilitate the regulation of energy intake and thus of body weight. For example, hypothalamic proopiomelanocortin (POMC) neurons act to inhibit appetite and food intake, in part by releasing agonists of the melanocortin 4 receptor. A novel, highly selective melanocortin 4 receptor agonist in development has been shown to chronically reduce food intake in a non-human primate model of obesity, without the unwanted effects on heart rate or blood pressure that such agents are often associated with (Kievit *et al.*, 2013). In addition, neurotransmitters including serotonin and the catecholamines are thought to act within appetite centres to modulate energy intake. In the USA, the Food and Drug Administration has recently approved two new centrally acting weight-loss drugs, Qsymia and Belviq, for use in adults with a BMI of over 30. Qsymia is a once-daily oral combination of phentermine, a sympathomimetic agent that antagonizes alpha-adrenergic receptors, and topiramate, an anti-epileptic agent believed to enhance the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) on excitatory glutamate neurons. Qsymia has beneficial effects on BMI, but has been associated with teratogenicity and an elevated heart rate, and does not have marketing approval in the UK thus far. The active ingredient of Belviq, lorcaserin hydrochloride, is a selective agonist of serotonin 5HT_{2C} receptors, which drives satiety through mechanisms which include stimulating POMC neurons (Heisler *et al.*, 2003). However, the precise mechanisms of action of such centrally acting drugs are rarely clear, with many displaying undesirable

side-effect profiles that reflect the fact that such signals do not usually exclusively control energy homeostasis. It is possible that following further assessment Qsymia and Belviq will be approved in Europe in the future. However, there are a number of other drug targets being investigated that may be useful in the long-term treatment of obesity.

Central and peripheral circuits work in tandem to tightly regulate energy homeostasis. The gut is the largest endocrine organ in the body, releasing over 20 peptide hormones which influence processes including gut motility, gastric acid secretion and energy intake. Sensing of macronutrients – fats, carbohydrates and lipids – in the gut modulates the secretion of appetite-regulating hormones which act via the vagus nerve or directly on the brain to alter food intake. These hormones include peptide YY (PYY) and glucagon-like peptide 1 (GLP-1), which are synthesized by enteroendocrine L-cells in the distal intestine and co-secreted into the circulation following a meal, and which act on specific brain regions to influence feeding behaviour. In addition, GLP-1 also stimulates glucose-stimulated insulin release. Interestingly, raised levels of such anorectic hormones are observed following bariatric surgery, and have been suggested to be responsible for at least part of the weight loss associated with this surgery. Such hormones represent peripheral signals which influence a relatively specific set of biological functions, and may thus result in fewer side-effects than other centrally acting agents. However, they also have short circulating half-lives, and thus the molecules require modification to be therapeutically useful.

Long-acting agonists of the GLP-1 receptor, for example liraglutide, are currently approved for the treatment of type 2 diabetes in the UK and USA. However, in addition to beneficial effects on glucose homeostasis, treatment with GLP-1 receptor agonists also results in weight loss, leading to trials of such agents as anti-obesity drugs. Concerns regarding a possible association with pancreatitis and pancreatic cancer have led to caution regarding the expansion of the use of GLP-1 agonists, but the EMA and FDA have recently stated that such causal associations 'are inconsistent with the current data'. Another possible use of GLP-1 agonists is to improve the targeting of other agents. Oestrogen is known to have beneficial metabolic effects in the brain, but also results in changes to reproductive organs when peripherally administered. A recent paper used a peripherally administered glucagon-like peptide-1 (GLP-1)–oestrogen conjugate to specifically deliver oestrogen to appetite-regulating regions of the brain, resulting in weight loss without the usual adverse effects on the reproductive system (Finan *et al.*, 2012).

In addition, our own research group is interested in the use of gut hormone analogues that can be administered weekly to regulate body weight, and have agents now progressing into phase 1 human clinical trials. Therapies combining several gut hormones may also prove to be successful, as some have been shown to have additive anorectic effects (Neary *et al.*, 2005). It may, for example, be possible to simulate some of the effects of bariatric surgery by infusing multiple gut hormones at the elevated levels observed following surgery, resulting in a so-called 'medical bypass'.

Postprandial levels of anorectic hormones, including PYY and GLP-1, are affected by the macronutrient composition of a meal. The physiology of the various nutrient-sensing receptors in the gut is gradually being elucidated, with receptors for sugars, fatty acids and amino acids now identified (Janssen & Depoortere, 2013). These receptors may represent better therapeutic targets than the hormones themselves, and 'functional foods' or 'nutraceuticals' designed to target them may prove useful in body weight management. High-protein diets, for example, lead to weight loss and improve weight maintenance, though they can be difficult to adhere to. Amino acids, the products of protein digestion, can modulate gut hormone release and may drive the increased satiety observed following protein ingestion. High protein meals have been shown to elicit greater and a more sustained PYY release than high fat or carbohydrate meals (van der Klaauw *et al.*, 2013) and specific amino acids may underlie these effects, with their administration in animal studies shown to reduce food intake and stimulate GLP-1 secretion (Fromentin *et al.*, 2012). However, the precise receptors or other sensing mechanisms involved are yet to be established.

In addition to pharmacotherapy, the effects of novel procedures that aim to replicate some of the effects of bariatric surgery without surgery are being studied. Examples include EndoBarrier™, which involves the insertion of synthetic apparatus which reduces the contact of ingested nutrients with the lining of the small intestine, and Obalon™, in which a balloon is inflated within the stomach to mimic the gastric distention felt after eating (Espinet-Coll *et al.*, 2012). Bariatric surgery also results in altered vagal signalling, and the vagus is known to play an important role in food intake, including communicating acute feelings of fullness to the brain. Severing the vagus leads to decreased food intake. Techniques in development, such as VBLOC, involve the implantation of electrodes intended to temporarily inhibit the transmission of hunger signals, decrease gastric distension and reduce secretion of enzymes, which it is hoped will lead to decreased nutrient absorption (EnteroMedics, 2014).

The methods mentioned above are thought to mainly act by reducing food intake or absorption, though some agents are also known to regulate energy expenditure. Brown adipose tissue (BAT), in comparison with the white adipose tissue that constitutes the majority of our fat reserves, is densely populated with mitochondria and heavily innervated by sympathetic nerve fibres. The ability to generate heat makes BAT important in non-shivering thermogenesis. Previously thought to be important only in newborn humans, BAT has recently been shown to be functional in adults, providing a new host of potential drug targets aimed at altering energy expenditure. Increasing BAT thermogenesis to burn off excess energy may present another mechanism of treating obesity, though further research is needed to determine the prevalence, distribution and functionality of BAT in obese humans, and the possible side effects of over-activating BAT (Tseng *et al.*, 2010).

Altering the way a person thinks about food and eating using cognitive behavioural therapy may also be a practical way to support lifestyle changes by improving coping skills and changing a person's perception of weight loss. With the continued and rapid development of technology, the trend of being permanently logged in to social media and documenting our day to day lives is increasingly prevalent. This has led to the development of hundreds of mobile 'apps' to complement dieting attempts, ranging from documenting food intake, receiving healthy living tips and offering self-support systems, to those purportedly providing on-the-go weight-loss hypnosis to those who require a little extra motivation to cut down their calorie intake.

Currently, successful lifestyle modification and education remain the most important factors in the management of obesity. However, they are ineffective in the majority of overweight and obese patients. The physiological systems that evolved in a very different environment to encourage excess energy storage appear difficult to manipulate in order to drive weight loss. Previously developed appetite-reducing agents have been fraught with safety issues, with a number of compounds withdrawn from the market. It is possible that targeting peripheral signalling systems, or more specific central circuits, may allow the development of drugs with improved safety profiles. Targeting multiple signals involved in energy homeostasis, similar to the way in which high blood pressure is often treated, may prove a promising tactic. It may be that a tailored programme of behavioural therapies, nutritional advice, functional foods and combination drug treatments is required to result in effective and sustained weight loss. While the development of such therapies is challenging, it is crucial to prevent the current obesity pandemic escalating even further out of control.

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A tale of three cities: the discovery of sodium/calcium exchange and some of its cardiovascular implications

How squid axons, frog muscles and the sodium/calcium exchanger built the foundation of a lifelong friendship and research collaboration.

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‘Here was the answer to a conundrum that puzzled me as a student and intern’

‘It was the best of times’. Reminiscences, by two of the participants, of a most fortuitous and improbable set of events that took place in the Autumn of 1966: the simultaneous and completely independent discovery of the sodium/calcium exchanger (NCX) in England and in Germany. This had a very felicitous fallout.

Plymouth, England, 1966: NCX in squid axons (MPB)

In August 1966, I completed my military service (studying lobster axons) at the Naval Medical Research Institute in Bethesda, Maryland. I was awarded an NIH Special Fellowship, and my family and I moved to Cambridge, England, where I intended to study squid axon electrophysiology with Alan Hodgkin. Upon arrival in Cambridge, I learned that Peter Baker, Alan’s young protégé, was taking a mini-sabbatical to study squid axon sodium pumps at the Laboratory of the Marine Biological Association in Plymouth. Peter, who was designated to oversee the foreign research fellows studying squid axons, wanted all of that season’s effort to focus on the sodium pump. That suited me because, while in medical school, I did research on red cell sodium pumps (Na,K-ATPase), on which I wrote my dissertation. Hence, after visiting Vienna for the International Biophysics Congress, I left my family in Cambridge and, in mid-September, travelled to Plymouth.

Richard (Rick) Steinhardt, Richard Keynes’s postdoctoral fellow, and I shared a lab. We agreed to determine how extracellular cations affect the sodium pump-mediated extrusion of Na⁺ ions from ²²Na⁺-injected squid giant axons. After teaching us how to use the axon microinjector equipment, Keynes left to help

teach a course on laboratory techniques at Homburg/Saar, Germany. Fortunately, I had prior experience dissecting squid axons in John Moore and Toshio Narahashi’s lab at Woods Hole, Massachusetts.

Within a week, Rick and I were obtaining reliable ouabain-sensitive (Na⁺ pump-mediated) Na⁺ efflux data. We then substituted dextrose for NaCl in the artificial sea water (ASW) bathing the axons. Unexpectedly, this induced a large, reversible Na⁺ efflux that was not mediated by the Na⁺ pump because it was not inhibited by ouabain or removal of external K⁺. Replacement of the NaCl by LiCl or choline Cl⁻ gave similar results. The reversibility indicated that this was not simply a ‘leak’ of Na⁺ with an anion. Peter, Rick and I reasoned that the Na⁺ efflux involved either co-transport of Na⁺ with an anion, or exchange of Na⁺ for an external cation (we had not yet replaced the external Ca²⁺ or Mg²⁺).

The simplest test was to remove the external divalent cations. First, we replaced the Ca²⁺ with Mg²⁺. That abolished the low Na⁺-induced large Na⁺ efflux (Fig. 1) – so we had our answer: Na⁺/Ca²⁺ exchange (NCX)! To verify the result, we also replaced Mg²⁺ with Ca²⁺, but that didn’t prevent the low Na⁺-ASW-induced Na⁺ efflux. What an exciting day – and I was barely a month into my fellowship! To prove the mechanism, however, we needed to demonstrate that the Na⁺ efflux

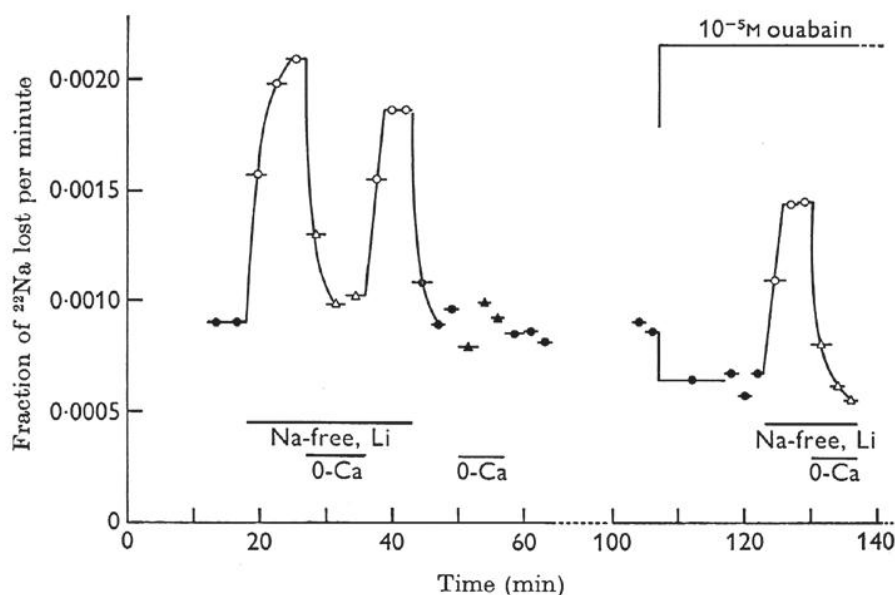


Figure 1. Reduction of the extracellular Na^+ concentration, $[\text{Na}^+]_o$, activates a large Ca^{2+} -dependent, ouabain-resistant $^{22}\text{Na}^+$ efflux in squid axons with a high intracellular Na^+ concentration, $[\text{Na}^+]_i$. Replacement of 460 mM NaCl in the artificial sea water (ASW) by LiCl greatly increased $^{22}\text{Na}^+$ efflux, measured as the fraction of $^{22}\text{Na}^+$ lost per minute. The increment was abolished by removal of the 11 mM CaCl_2 in the ASW (MgCl_2 was increased from 55 to 66 mM). This is evidence of ' Na^+ - Ca^{2+} antagonism', and indirect evidence for $\text{Na}^+/\text{Ca}^{2+}$ exchange. Ouabain (10^{-5} M) reduced the $^{22}\text{Na}^+$ efflux in control Na^+ -ASW (i.e. it inhibited the Na^+ pump), but it had no effect on the large external Ca^{2+} -dependent $^{22}\text{Na}^+$ efflux in Li^+ -ASW; right). Reprinted from Baker *et al.* (1969), with permission.

in low Na^+ -ASW was associated with a large Ca^{2+} influx, so we ordered ^{45}Ca .

I was becoming exhausted by the 14–16 hour work days, but was afraid to lose momentum; I had been warned that gales were often followed by a dearth of squid. A gale did intervene, however, in early November, so I could catch my breath, and even catch up on reading. Peter had mentioned Luttgau and Niedergeske's studies on Na^+ - Ca^{2+} antagonism in frog heart that he thought might be relevant to our work. With the lab deserted, I went down the hall to the library, and found their article (Luttgau & Niedergeske, 1958). They attributed the increased cardiac contraction in low- Na^+ Ringer's to a competition between external Na^+ and Ca^{2+} at the cell surface. Even before finishing the article, I realized that their results might also be explained by a cardiac NCX. Here was the answer to a conundrum that puzzled me as a student and intern: how does Na^+ pump inhibition by cardiotonic steroids such as digoxin and ouabain increase the force of cardiac contraction (the positive inotropic effect)? Obviously, NCX was the missing link: raising intracellular Na^+ should promote NCX-mediated net gain of Ca^{2+} , which should increase contraction efficiency (Baker *et al.*, 1969). I was ecstatic! I treated myself to a fine dinner and excellent bottle of claret. Then, two sheets to the wind, I returned to the lab to re-read Luttgau–Niedergeske, just to be sure I wasn't delusional. Another great day!

The ^{45}Ca arrived at the end of the week, and Alan arrived the next Monday to see how I was getting on. At dinner, Alan listened intently as I described the data and our thoughts about their significance – but he gave no hint of whether he bought the NCX story. During the next two days, he dissected axons and

modelled our data, while I set up for the Ca^{2+} influx experiments. Then, on Thursday, he asked if I would mind if he stayed in Plymouth for the Ca^{2+} influx experiments. Would I mind? I was thrilled – we'd won him over!

The next Monday, Alan and I performed the first Ca^{2+} influx experiment. Axon segments, tied at both ends, were incubated in ^{45}Ca -labelled normal (Na^+)-ASW or Li^+ -ASW. The axons were then washed and axoplasm was extruded with a miniature garden roller, weighed, dried on a planchet, and the radioactivity was counted. The first Na^+ -ASW axon sample gave a low count. The second was from a Li^+ -ASW axon, and the Panax counter nixie tubes flashed away (i.e. Ca^{2+} influx was much greater; Table 1). Alan broke into a broad grin; he could hardly wait to count the next samples – $\text{Na}^+/\text{Ca}^{2+}$ exchange was proven! When the counts were completed (long past midnight), we celebrated with 'medicinal' Scotch.

As Table 1 illustrates, we were very lucky. It was difficult to keep large squid alive. Therefore, while at sea, the laboratory fishermen removed the heads and placed the squid mantles in large thermoses containing iced sea water. Several hours later, we dissected the axons and started the experiments, but while the Na^+ pumps were inhibited by the icy temperature, the axoplasm Na^+ concentration slowly rose. This greatly augmented $\text{Na}^+/\text{Ca}^{2+}$ exchange compared to results from live squid axons (Table 1); we couldn't miss the large flux differences.

The experiments continued until Christmas (end of the squid season), and through the 1987 squid season. We recognized that a 2 $\text{Na}^+:\text{Ca}^{2+}$ exchange would not drive intracellular Ca^{2+} ($[\text{Ca}^{2+}]_i$) below 10 μM , and

anticipated that $[\text{Ca}^{2+}]_i$ was actually lower than this. The $\text{Na}^+:\text{Ca}^{2+}$ stoichiometry data were inconclusive, but suggested that the coupling ratio was $>2 \text{ Na}^+:\text{Ca}^{2+}$ (Baker *et al.*, 1969; Blaustein & Hodgkin, 1969).

Sadly, Peter Baker died prematurely, in 1987, just before the First International Meeting on NCX, which he planned, was convened in Stowe, England. The conference and proceedings became a memorial to Peter.

Mainz, Germany, 1966: NCX in the heart (HR)

My interest in 'calcium and the heart' began when I was an assistant in the Institute of Pharmacology at the University of Mainz, Germany. At that time very little was known about how Ca^{2+} could be involved in the beating of the heart although already in 1883 Sidney Ringer had shown that Ca^{2+} was essential for the beating of the frog heart (Ringer, 1883). When Silvio Weidmann, a founder of the microelectrode technique in cardiac muscle, invited me to come to the Institute of Physiology at the University of Bern, I started searching for an electrophysiologically measurable membrane current carried by Ca^{2+} ions in cardiac Purkinje fibres. I was lucky to discover such a current that was Ca^{2+} dependent and contributed to the plateau phase of the cardiac action potential and was increased by adrenaline (Reuter, 1967). This current (now called L-type Ca^{2+} -current), its essential role in the heart beat, its molecular properties, and its regulation by neurotransmitters and drugs, became a major focus of my further scientific investigations.

If Ca^{2+} enters cardiac cells during excitation, a logical consequence was that some ' Ca^{2+}

‘It became quickly apparent that reduction of Na⁺ in the external solution greatly diminished ⁴⁵Ca efflux from the auricles. I was delighted that my idea of a ion exchange seemed to be correct’

Table 1. Effects of external cations and of ouabain on ⁴⁵Ca influx in squid axons. Reduction of the external Na⁺ concentration, [Na⁺]_o, increased ⁴⁵Ca influx. This is evidence of ‘Na⁺–Ca²⁺ antagonism’ at the cell surface. The increase in Ca²⁺ influx was much greater in the axons from refrigerated squid mantles (with a high intracellular Na⁺ concentration, [Na⁺]_i) than in axons from live squid (with a lower [Na⁺]_i). This is direct evidence of Na⁺/Ca²⁺ exchange. Data from Baker *et al.* (1969).

A. Axons from refrigerated mantles

Collected results*:

External solution	Ca influx (pmol cm ⁻² sec ⁻¹)		n
	Mean ± S.E.	Range	
Na ⁺ –ASW, 0 and 10–K, ± ouabain	0.15 ± 0.02	0.04–0.57	30
Li ⁺ –ASW, 0 and 10–K, ± ouabain	4.33 ± 0.43	0.90–9.50	29
Dextrose ASW, 0 and 10–K, ± ouabain	2.46 ± 0.29	0.80 – 5.30	15

B. Axons from live squid

10–K, Na ⁺ –ASW	0.23	—	1
10–K, Li ⁺ –ASW	0.66 ± 0.48	0.16–1.60	3

n is the number of axons in each group. * Li⁺–ASW (artificial sea water) contained 460 mM LiCl in place of NaCl; dextrose ASW contained 720 mM dextrose in place of 460 mM NaCl. In K-free (‘OK’) ASW, the 10 mM KCl was replaced by 10 mM NaCl or LiCl, or 20 mM dextrose. Because neither replacement of external K⁺ nor addition of 10⁻⁵ M ouabain affected the Ca²⁺ influx, the OK and ouabain treatment data were not separated.

pump’ had to extrude the ions from the cells against an electrochemical gradient. Schatzmann (1966) had shown the existence of ATP-dependent Ca²⁺ extrusion from human red blood cells. However, no such extrusion mechanism had so far been shown to exist in heart cells. Only several years later could Caroni & Carafoli (1981) demonstrate a Ca²⁺–pumping ATPase in cardiac cell membranes.

In September 1966, I attended a course on ‘Laboratory Techniques in Membrane Biophysics’ organized by Hermann Passow and Robert Stämpfli in Homburg/Saar, Germany. Under the direction of Peter Caldwell and Richard Keynes, the students had to do ²²Na radiotracer flux experiments in isolated frog muscle. Those experiments

showed an electroneutral Na⁺/Na⁺ exchange across the membrane that was explained by a carrier transport energetically driven by the electrochemical Na⁺–gradient. Hans Ussing first described this phenomenon, and called it ‘exchange diffusion’. During the membrane course Aharon Katchalsky gave a series of lectures on irreversible thermodynamics related to membrane transport. Low energy costs of Na⁺/Na⁺ exchange were mentioned by him and evoked my idea that perhaps Na⁺/Ca²⁺ instead of Na⁺/Na⁺ exchange diffusion could possibly be a transport mechanism of Ca²⁺ across the cardiac cell membrane. In contrast to Na⁺/Na⁺ exchange, Na⁺/Ca²⁺ exchange might provide a net transport for both ions, for example by exchanging extracellular Na⁺ against intracellular Ca²⁺.

Figure 1 consists of two vertically stacked line graphs. Both graphs plot the 'Rate coefficient k (min^{-1})' on the y-axis against 'Minutes' on the x-axis. The x-axis has major ticks at 0, 60, 120, 180, 240, and 300 minutes. The top graph's y-axis ranges from 0 to 0.04, while the bottom graph's y-axis ranges from 0 to 0.02. Both graphs show a series of data points connected by a line, with vertical bars indicating experimental error. The data points are labeled with the concentrations of Ca^{2+} and Na^{+} in mM. The top graph shows a decrease in k as $[\text{Ca}^{2+}]_o$ increases from 0 to 1.8 mM, and a sharp increase in k as $[\text{Na}^{+}]_o$ increases from 0 to 149 mM. The bottom graph shows a similar trend, with k decreasing as $[\text{Ca}^{2+}]_o$ increases and increasing as $[\text{Na}^{+}]_o$ increases.

Minutes	$[\text{Ca}^{2+}]_o$ (mM)	$[\text{Na}^{+}]_o$ (mM)	Rate coefficient k (min^{-1})
0	0	149	0.035
10	0	149	0.021
20	0	149	0.015
30	0	149	0.012
40	0	149	0.011
50	0	149	0.011
60	0	149	0.011
70	1.8	149	0.031
80	1.8	149	0.021
90	1.8	149	0.018
100	1.8	149	0.016
110	1.8	149	0.014
120	1.8	149	0.012
130	1.8	149	0.010
140	1.8	149	0.008
150	1.8	149	0.007
160	1.8	149	0.006
170	1.8	149	0.004
180	0	0	0.002
190	0	0	0.002
200	0	0	0.002
210	0	0	0.002
220	0	0	0.002
230	0	0	0.002
240	1.8	149	0.021
250	1.8	149	0.015
260	1.8	149	0.012
270	1.8	149	0.010
280	1.8	149	0.009
290	1.8	149	0.008
300	1.8	149	0.007
310	1.8	149	0.006
320	1.8	149	0.005
330	1.8	149	0.005
340	1.8	149	0.005
350	1.8	149	0.005
0	0	149	0.015
10	0	149	0.009
20	0	149	0.007
30	0	149	0.006
40	0	149	0.005
50	0	149	0.004
60	0	149	0.004
70	1.8	149	0.008
80	1.8	149	0.007
90	1.8	149	0.006
100	1.8	149	0.006
110	1.8	149	0.006
120	1.8	149	0.006
130	1.8	149	0.005
140	1.8	149	0.004
150	1.8	149	0.004
160	1.8	149	0.004
170	1.8	149	0.003
180	0	0	0.002
190	0	0	0.002
200	0	0	0.002
210	0	0	0.002
220	0	0	0.002
230	0	0	0.002
240	1.8	149	0.007
250	1.8	149	0.006
260	1.8	149	0.006
270	1.8	149	0.006
280	1.8	149	0.006
290	1.8	149	0.004
300	1.8	149	0.003
310	1.8	149	0.003
320	1.8	149	0.003
330	1.8	149	0.003
340	1.8	149	0.003
350	1.8	149	0.003

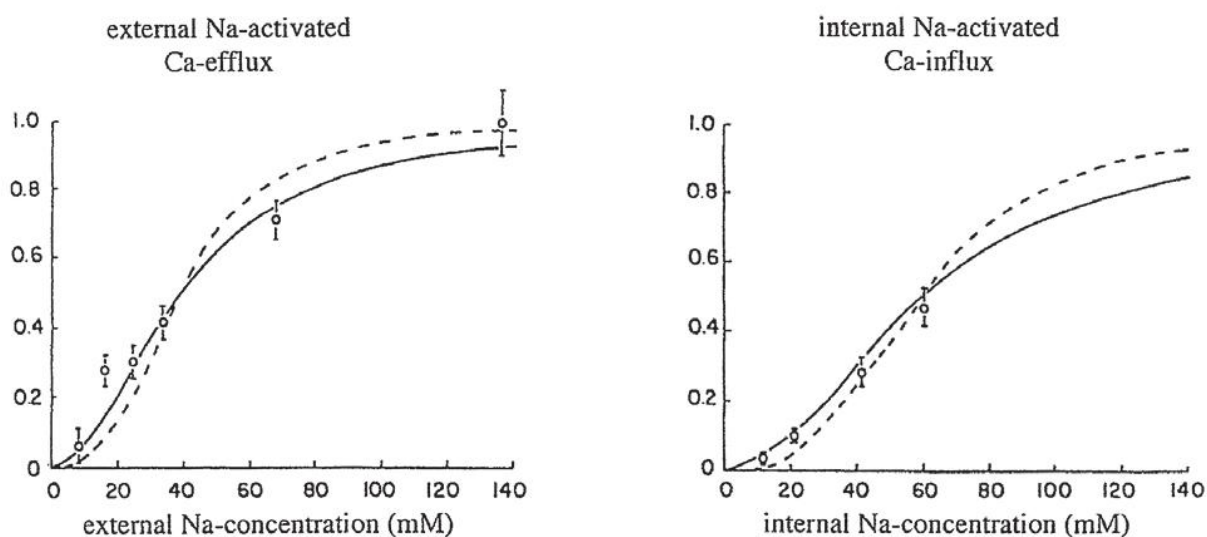


Figure 3. Fractions of Ca²⁺ efflux and influx in guinea pig auricles depending on external and internal Na⁺ concentrations, respectively. Data replotted from Reuter & Seitz (1968) (left), and Glitsch *et al.* (1970) (right) assuming exchange stoichiometries of 2 Na⁺:1 Ca²⁺ (continuous lines) and 3 Na⁺:1 Ca²⁺ (dashed lines).

concentration in the auricles rose when external Na^+ was replaced by Li^+ or sucrose and was reduced again when Na^+ was readmitted. Metabolic inhibitors increased rather than decreased the rate of ^{45}Ca efflux, in agreement with a relatively low energy demand of an exchange diffusion process, where Ca^{2+} extrusion from the cells depends on the Na^+ and Ca^{2+} gradients across the cell membrane. The total ^{45}Ca efflux could be divided into a Na^+ - and a Ca^{2+} -dependent fraction. Assuming a competition of 1 Ca^{2+} and 2 Na^+ ions for promoting Ca^{2+} efflux, a concentration ratio of $[\text{Ca}^{2+}]/[\text{Na}^+]^2$ in the external medium seemed to provide a good fit to the data (Reuter & Seitz, 1968) (Fig. 3). I was misled, however, by this assumption in terms of the true stoichiometry of the exchanger.

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‘Although Rolf Niedergerke was rather skeptical, my concept of $\text{Ca}^{2+}/\text{Na}^{+}$ exchange in the heart was generally quickly accepted’

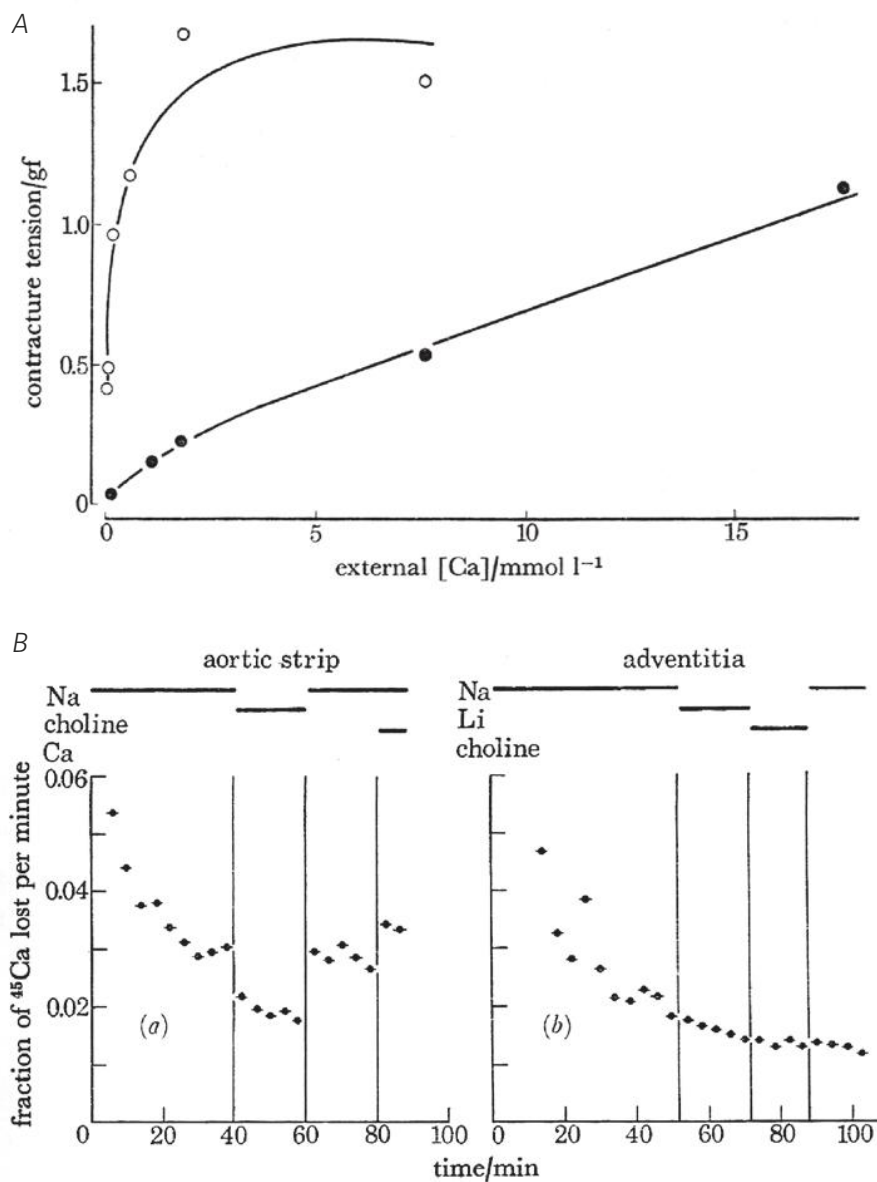


Figure 4. A, effect of the external Ca^{2+} concentration, $[\text{Ca}^{2+}]_o$, on contraction of rabbit aorta. Contractile tension (gf) was increased by reduction of $[\text{Na}^{+}]_o$. Either 80% (filled circles) or 100% (open circles) of the NaCl in the standard medium (137 mM) was replaced by equiosmotic sucrose. The greater effectiveness of low $[\text{Ca}^{2+}]_o$ in inducing contraction when $[\text{Na}^{+}]_o$ was lowered is evidence of ' $\text{Na}_o\text{-Ca}_o$ antagonism'.

B, reduction of $[\text{Na}^{+}]_o$ decreased $^{45}\text{Ca}^{2+}$ efflux (fraction of $^{45}\text{Ca}^{2+}$ lost per min) in a rabbit aortic strip (left), but not in the isolated adventitia (right). The NaCl in the standard medium (137 mM) was replaced by equimolar LiCl or choline-Cl during the periods indicated by the bars at the top. To avoid influx of Ca^{2+} and dilution of intracellular tracer $^{45}\text{Ca}^{2+}$, the efflux (extracellular) solutions were Ca-free and contained 0.5 mM EGTA, except during the period indicated by the 'Ca' bar at the end of the experiment on the left. The external Na^{+} -dependent $^{45}\text{Ca}^{2+}$ efflux in intact aortic strip is evidence of $\text{Na}^{+}/\text{Ca}^{2+}$ exchange. Reprinted from Reuter *et al.* (1973), with permission.

Exchange of 2 Na^{+} for 1 Ca^{2+} is energetically insufficient to reduce the internal Ca^{2+} concentration, which was not known at that time, to 0.1 μM or less. Later experiments by John Reeves and Calvin Hale (1984) with cardiac membrane vesicles showed clearly a coupling ratio of 3 Na^{+} ions for 1 Ca^{2+} . Thus the exchanger is electrogenic as shown by

Junko Kimura and colleagues (1987). The story culminated with the cloning of the exchanger molecule by Ken Philipson (Nicoll *et al.*, 1990).

If the driving force for net Ca^{2+} extrusion from the cells depends on the Na^{+} gradient across the cell membrane, reduction of the Na^{+} gradient by elevating the internal Na^{+}

concentration, e.g. by manipulating the external K^+ concentration, or by inhibiting the $Na^+,K^+-ATPase$ (Na^+ pump) by cardiac glycosides, should reduce Ca^{2+} efflux from the cells. This was, indeed, shown two years later by Glitsch, Reuter & Scholz (1970). These experiments were influenced by the squid axon studies (Baker *et al.*, 1969). Incidentally, Hodgkin later told me, at the 1987 meeting in memory of Peter Baker, that he reviewed the Reuter & Seitz paper (1968) for *The Journal of Physiology*; he graciously recommended it for publication without revision. Although Rolf Niedergerke was rather skeptical, my concept of Ca^{2+}/Na^+ exchange in the heart was generally quickly accepted.

Bern, Switzerland, 1971: NCX in vascular smooth muscle (MPB & HR)

In August 1968, Blaustein accepted a faculty position at Washington University, his alma mater. He and his family moved from Cambridge to St Louis, Missouri, with a stop in Washington, DC, for the International Physiology Congress, where Reuter and Blaustein first met. This was the start of a long-lasting friendship.

In 1971 Blaustein and Reuter arranged a collaboration. The choice of venue (St Louis or Bern in late-spring and summer) was a

'no-brainer', so Blaustein obtained a NATO Fellowship and arranged for a mini-sabbatical, and the family headed for Switzerland. Bern also enabled them to re-connect with their Cambridge neighbours, Mani (lawyer, Bern Town Counsel and composer) and Joy Matter.

Reuter suggested that they determine whether arterial smooth muscle (ASM) has a Na^+/Ca^{2+} exchanger – a proposal to which Blaustein readily agreed. Günther Haeusler, a vascular smooth muscle expert from Hoffmann-LaRoche, Basle, taught us how to dissect strips of rabbit thoracic aorta, in which we then measured total Ca content, ^{45}Ca fluxes and tension. The first experiments demonstrated Na^+-Ca^{2+} antagonism: reducing extracellular Na^+ increased Ca content and enhanced contraction (Fig. 4A). We then showed that Ca^{2+} efflux from ^{45}Ca -loaded aortae, but not isolated adventitia, was external Na^+ dependent (Fig. 4B). Thus, ASM has a NCX mechanism that helps to regulate intracellular Ca^{2+} and arterial contraction (Reuter *et al.*, 1973). We postulated that there is a close approximation between the NCX in the plasma membrane (PM) and the Ca^{2+} pumps in the sarcoplasmic reticulum (SR). This foreshadowed Van Breemen's 'buffer-barrier' hypothesis (Chen *et al.*, 1992) and Blaustein's 'PLasmERosome' model of local Ca^{2+} control (Blaustein *et al.*, 1998).

We also raised the possibility that NCX might not only help regulate vascular tone, but also contribute to the pathogenesis of hypertension. Unfortunately, the vascular smooth muscle community was reluctant to accept the Blaustein-Reuter data and ideas. The manuscript was therefore published in a non-refereed journal (Reuter *et al.*, 1973) when Reuter was asked by Edith Bülbring to participate in a conference sponsored by the Royal Society.

Despite this skepticism, the experiments in Bern marked a turning point in Blaustein's career, and he began to focus on Ca^{2+} regulation in ASM and hypertension (Blaustein, 1977). The Blaustein-Reuter ideas about the role of NCX in ASM were vindicated by immunoblot identification and immunocytochemical localization of NCX at 'PM-SR junctions' in ASM (Juhaszova *et al.*, 1994). Indeed, NCX apparently plays a key role in cardiovascular physio-pathology. NCX is greatly over-expressed in cardiomyocytes during heart failure, where it promotes Ca^{2+} extrusion and likely contributes to left ventricular dysfunction (Studer *et al.*, 1994; O'Rourke *et al.*, 1999), and in arterial myocytes in many models of hypertension, where it promotes Ca^{2+} entry and vasoconstriction (Blaustein *et al.*, 2012).

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Translational physiology in practice

'Knowing is not enough; we must apply. Willing is not enough; we must do'
Johann Wolfgang von Goethe

*Douglas Seals,
Jessica Santos-Parker
& Thomas LaRocca*

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University of Colorado, USA

'Fortunately, many functions can now be modelled and studied using translation-friendly techniques in preclinical models and human subjects'

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Translational research has become the preferred model worldwide for organizations supporting biomedical science. As a field, we should look for opportunities to integrate translational approaches into physiological research to most effectively gain insight into mechanisms of interest, study relations between genotype and phenotype, establish the efficacy of interventions, and maximize the impact of our work on public health.

Translational research has received a lot of attention in some corners of the biomedical research community over the past decade. Traditionally, translational research has been viewed as a process in which experimental observations made at the basic science level using preclinical models (cell culture and animal models) are eventually tested in humans. However, contemporary views of translational research emphasize a dynamic 'continuum' of observations from basic science to the clinical research setting ('T1 translation'), then to medical practice/clinical guidelines ('T2 translation') and, finally, to the community, where the findings serve to inform public health policy ('T3 translation') (Fig. 1). This process should operate *bi-directionally*, i.e. observations made initially in populations or in medical practice can be 'reverse translated' to gain insight into mechanisms of action via controlled studies performed in a clinical research centre or basic research laboratory (Fig. 1). Because research at these various levels requires different skill sets, personnel and infrastructure, it often involves multi-disciplinary collaborations. The importance of translational research is reflected by the recent establishment of the new translational offices and programmes within biomedical research organizations in the EU and worldwide, including the National Center for

Advancing Translational Science in the US. (www.ncats.nih.gov).

There is a growing demand for translational research in physiology. In the following sections, we discuss this important need and how our laboratory approaches translational physiological research.

Translational physiology

Physiology, the study of function of living organisms, can be effectively investigated using translational strategies. Indeed, since a pivotal initial commentary by John Hall in 2002 (Hall, 2002), several editorials have emphasized the need for translational approaches in physiology. What wasn't clear in these commentaries, however, was exactly *how* to apply translational research practices in physiological research. To help address this question, we recently published a full-length perspective on the topic (Seals, 2013). In that article, we advanced the concept of translational physiology as a framework to study function from molecular events all the way up to informing public health policy, with the ultimate goal of attaining optimal physiological function in populations of both healthy adults and patients with clinical disorders (Fig. 2). Key concepts, experimental approaches, opportunities, roadblocks and

Translational Research Continuum

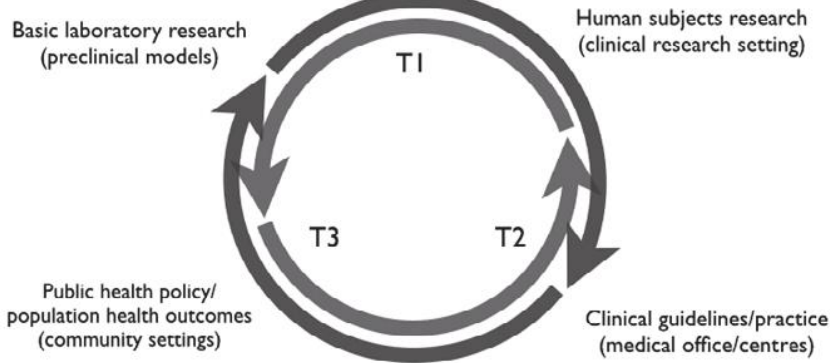


Figure 1. The dynamic and bi-directional translational research continuum. Observations from basic science (T1) can be translated to the clinical research setting and eventually applied in clinical practice (T2) and public health policy (T3). Alternatively, T3 or T2 observations may be used to drive discovery or investigations of underlying mechanisms at the T1 level. Reproduced from Seals (2013).

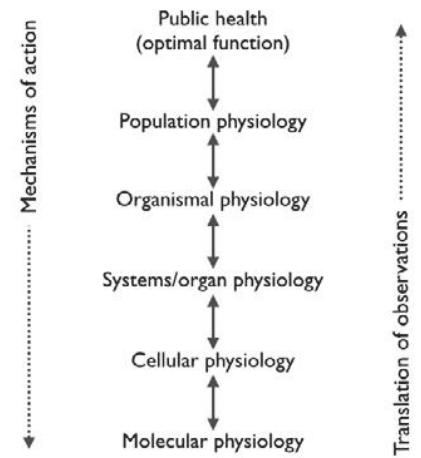


Figure 2. A framework for translational physiology. Physiological function can be studied from molecular events to public health with the goal of optimizing function in healthy adults and patients with clinical disorders. Reproduced from Seals (2013).

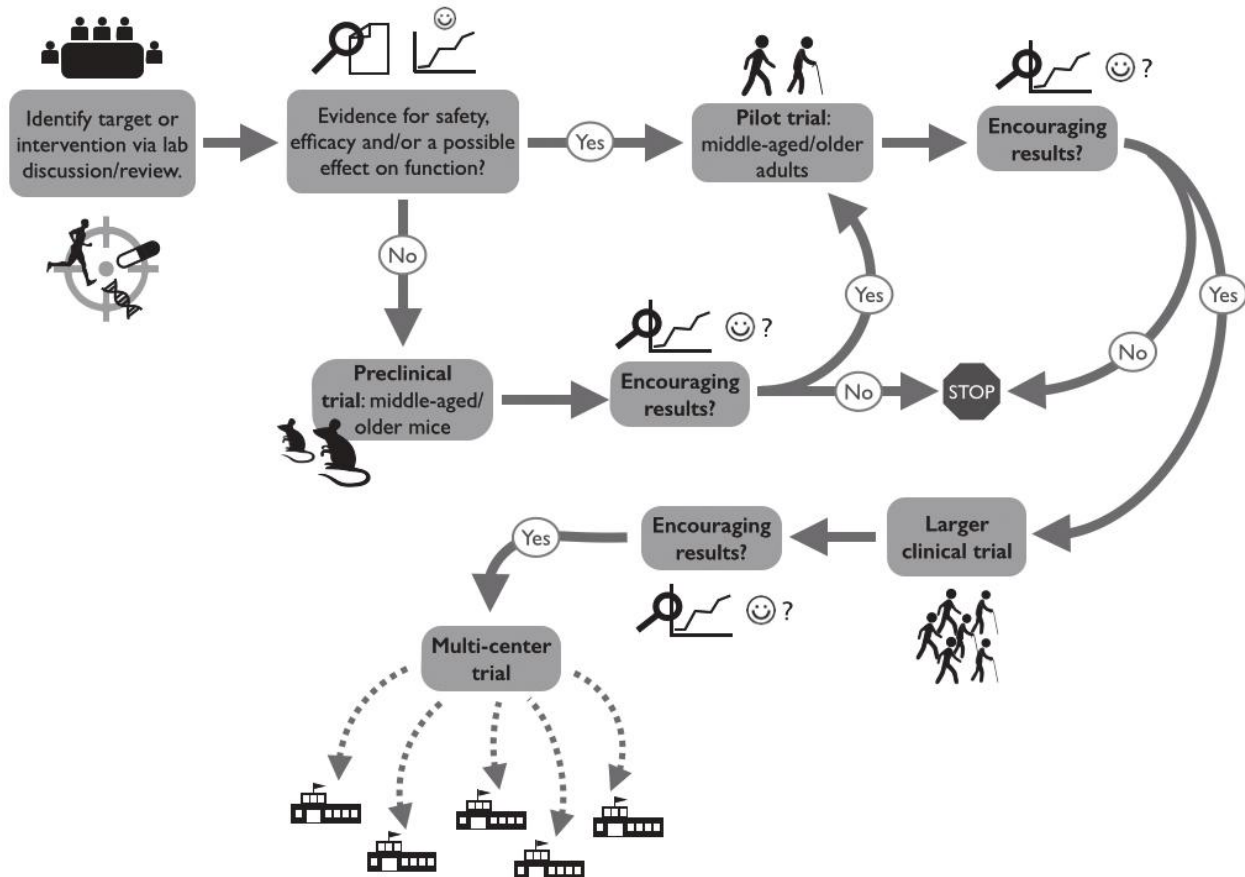


Figure 3. One possible approach to translational physiology. We identify potential targets or interventions that may improve physiological function during ageing, and evaluate them for translational potential. If they appear promising, we may proceed directly to pilot clinical trials; otherwise, we might first test for efficacy in preclinical studies in mice. In either case, experimental results are used to inform our decision about how and if to proceed to higher levels of translation, with the ultimate goal of identifying therapies and interventions with the potential for broad application.

'Translational physiology offers new opportunities for studying function from molecular events to populations of humans, with direct relevance to clinical practice and public health'

strategies for success all were discussed in some detail.

As noted in our paper (Seals, 2013), several compelling examples of successful translational investigations in physiology already exist, one of which is the study of dietary sodium intake and arterial blood pressure. Following the discovery of a relation between dietary sodium and blood pressure in human populations in the early 1960s, a series of 'upward' translational investigations were performed culminating in studies of dietary sodium restriction for reducing blood pressure in various groups. These findings led to the establishment of new clinical guidelines for daily sodium intake, as well as to changes in public health policy in some countries to reduce sodium in processed foods. At the same time, the epidemiological observations stimulated *reverse* translational studies of mechanisms underlying the effects of sodium intake on blood pressure in both clinical and preclinical models. Thus, over the past 50+ years, the full translational scope of investigation from T1 to T3 has been conducted on this clinically relevant issue in physiology.

Unprecedented opportunities

Today, there are unprecedented opportunities to conduct translational physiological research on a large scale. The ability to manipulate genes and signalling pathways in cells and experimental animal models has revolutionized basic research in biology, including physiology. Similarly, recent developments in high throughput molecular analysis ('omics') and systems biology, combined with the wide availability of samples from human subjects, is creating new horizons for conducting investigations in population physiology. With these novel technologies, we are in a position to bridge key gaps in translational research by combining insight from several domains of investigation, including mechanisms of physiological function and dysfunction, variability in subjects' baseline function and responses to stress/intervention, and the relations between genotype and phenotype (Seals, 2013). Utilizing new developments in molecular analysis of biological samples and non-invasive physiological monitoring, along with established observational approaches, will allow us to extend investigation of physiology from cells, tissues and individual organisms to populations of humans. In so doing, we can expand the traditional boundaries of clinical epidemiology (population health and disease) to 'physiological epidemiology' (population function) (Seals, 2013). Extending our scope of study to populations also will provide opportunities to better determine how the environmental factors to which we are chronically exposed (aging, education, income, social networks, culture, pollution,

etc.) influence human physiology, functional status, disease risk and mortality.

Translational physiology in practice: assessing interventions to improve function

One important application for translational research, including translational physiology, is the need to develop new strategies to prevent and treat clinical diseases and delay adverse ageing processes. Our laboratory, for example, is interested in optimizing and preserving physiological function during adult ageing with the ultimate goal of extending healthy lifespan ('healthspan'). The need for this work is reflected by the strong interest in the biomedical industry to advance drugs for treating age-associated diseases. This is an extensive process requiring efforts throughout the translational continuum, from identifying promising signalling pathways, developing screening tests for compounds that may activate (or inhibit) those pathways, screening numerous compounds, and eventually testing for safety and efficacy in preclinical models and then in humans (Collis, 2013). Conventional drug development increasingly has become a prohibitively lengthy and expensive process, involving resources far beyond the scope of academic physiology laboratories. As such, we have adopted our own translational physiological research approach for establishing effective strategies to preserve function with ageing. Most of our work over the past decade has involved assessing the effectiveness of various interventions for improving vascular function in late middle-aged and older (MA/O) adults with baseline dysfunction. We test the efficacy of both healthy lifestyle behaviours and novel nutraceutical compounds with potentially healthy lifestyle-'mimicking' effects for enhancing physiological function with ageing. To accomplish this, we employ a variety of translational approaches, beginning with the original idea and advancing to clinical trial testing.

One laboratory's approach

Our approach begins by identifying lifestyle behaviours (most often, exercise, energy intake or diet composition) or pharmacological compounds that might improve function during ageing (Fig. 3). If there is sufficient evidence for safety and possible efficacy (i.e. improvement in function) in the scientific literature, the intervention can be directly tested in MA/O adult humans. If not, preclinical studies are performed in MA/O mice to obtain such evidence. If the results are encouraging, we then develop protocols for testing the treatment in human subjects.

In our work, ideas for investigation are based on identifying possible therapeutic targets and interventions that may influence (activate/inhibit) those targets. There are

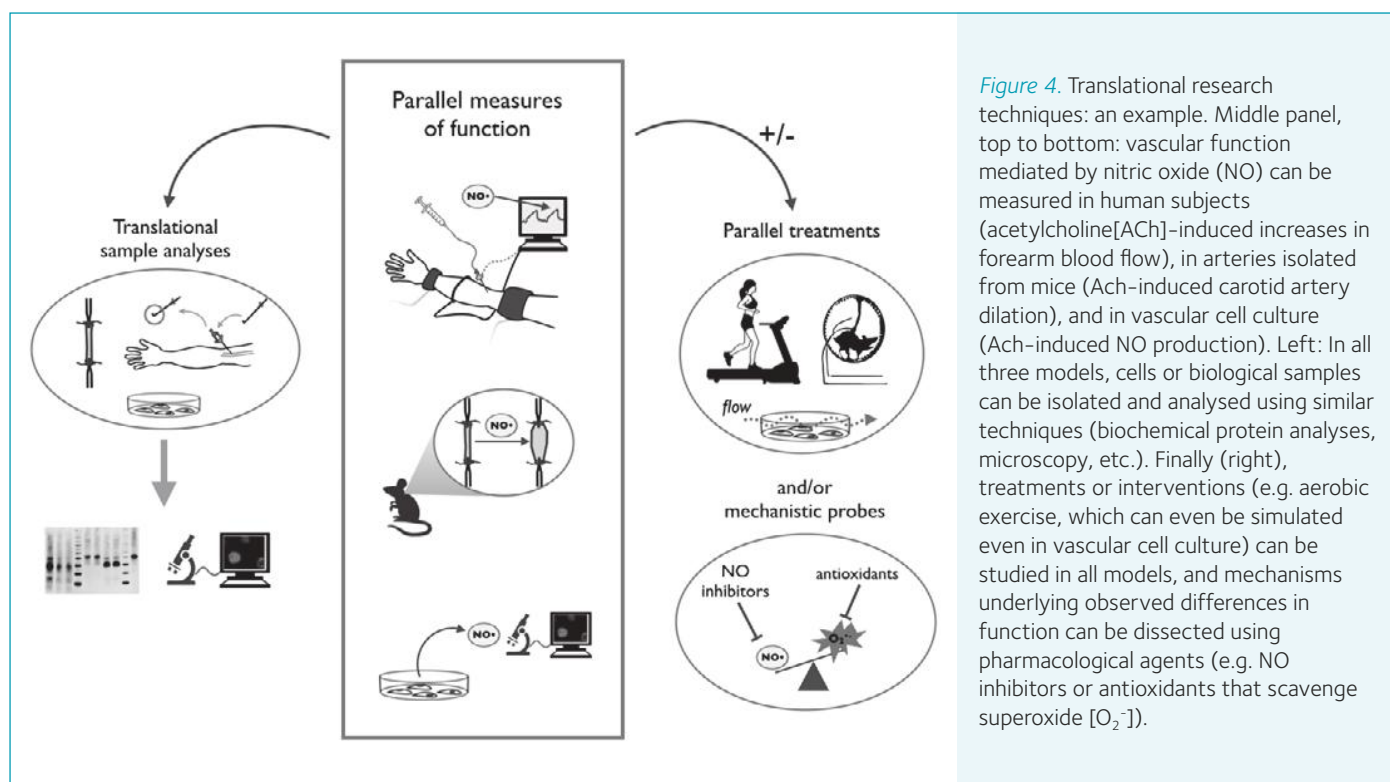


Figure 4. Translational research techniques: an example. Middle panel, top to bottom: vascular function mediated by nitric oxide (NO) can be measured in human subjects (acetylcholine[ACh]-induced increases in forearm blood flow), in arteries isolated from mice (ACh-induced carotid artery dilation), and in vascular cell culture (ACh-induced NO production). Left: In all three models, cells or biological samples can be isolated and analysed using similar techniques (biochemical protein analyses, microscopy, etc.). Finally (right), treatments or interventions (e.g. aerobic exercise, which can even be simulated even in vascular cell culture) can be studied in all models, and mechanisms underlying observed differences in function can be dissected using pharmacological agents (e.g. NO inhibitors or antioxidants that scavenge superoxide $[O_2^{\cdot-}]$).

several sources for ideas. We draw heavily from the basic science literature. Indeed, although we are considered a translational research laboratory, most of the papers discussed in our weekly laboratory meeting/ journal club involve basic research, both original research articles and reviews. We attempt to identify, early on, novel molecular/cellular signalling pathways that modulate our physiological function of interest, as well as compounds that could be used to induce the desired effect on those pathways and improve function. In many cases, the signalling pathway of interest may not have been shown previously to influence function *per se* (e.g. improve vascular endothelial function), but rather to alter a key determinant of that function (e.g. increase nitric oxide [NO] bioavailability). This approach requires constant surveillance and assessment of the translational potential of a dynamic, continually expanding scientific literature based on genetic and molecular biological observations, i.e. a literature that often supersedes our technical expertise and intellectual comfort zone. Nevertheless, we have found basic research to be a rich source of ideas for innovative translational studies. To facilitate this process, we seek students and postdoctoral fellows from a range of backgrounds: biochemistry to clinical research to the pharmaceutical industry. Once in the laboratory, trainees become informed on topics of interest from a basic science perspective up to community health, and develop the research and intellectual skills necessary to conduct their work using translational research principles.

In the end, potential therapeutic targets and

interventions can be identified from observations made at the preclinical, clinical or even *epidemiological* (population) levels. Referring to the earlier example, the epidemiological finding of a relation between dietary sodium intake and blood pressure led to trials testing the efficacy of dietary sodium restriction for lowering blood pressure in patients with essential hypertension (Mozaffarian *et al.*, 2011). Similarly, clinical trials and mechanistic investigations on the potential benefits of omega-3 fatty acid supplementation were triggered by epidemiological observations in native Eskimo populations (Mozaffarian *et al.*, 2011). Ideas also can be generated from findings not directly related to the function of interest. In our work in vascular ageing, we may explore the efficacy of an intervention that has been shown to improve insulin resistance in patients with type 2 diabetes mellitus, or extend lifespan in *C. elegans* or other basic models of ageing. The essential question in these situations is whether or not the putative treatment likely influences a key biological process modulating the target function.

When considering a possible intervention stemming from work in preclinical models, it is important to consider the feasibility for translation to humans. Is there a synthetic or natural version of the compound that can be delivered to human subjects at a dose and for a duration that would be both safe and effective? For physiologists interested in improving function in humans, determining the regulatory/approval status of the agent also is important to consider. In our laboratory, if there is no obvious compound that is either already approved for use in

humans or that could be approved by an institutional review board in a timely manner, generally we do not expend the time, effort and resources to conduct preclinical studies on that agent. The ultimate goal must be to test efficacy in trials on humans because of the high historic rate of 'false positive' findings when studies in preclinical models are tested in humans. Many basic science laboratories establish preclinical evidence for a therapeutic target and, in some cases, a possible treatment compound, and then move on to the next potential target. However, full translational assessment of a treatment to improve and/or preserve physiological function requires establishing efficacy in human populations.

Fortunately, many functions can now be modelled and studied using translation-friendly techniques in preclinical models and human subjects. In our work, similar measurements of vascular function (including endothelium-dependent dilation and large elastic artery stiffness) can be made in mice, physiological studies of small groups of healthy adults, and larger clinical trials (Donato *et al.*, 2011; LaRocca *et al.* 2012; Seals, 2013). The same is true for muscle function, glucose-insulin signalling, metabolism and many other areas in physiology. Integrative motor function assessment batteries used in physiological, clinical and epidemiological investigations in humans can be modelled in rodents (Justice *et al.*, 2014), and continuous *in vivo* monitoring of numerous physiological variables can be conducted using telemetry in animal models and contemporary sensor technology in human populations.

Translational insight into mechanisms of action

Several options are available to investigate mechanisms of action using translational approaches. As an example (Fig. 4), in an initial study of a potential therapy for vascular ageing using our mouse model, function in arteries from treated and untreated animals can be assessed *ex vivo* in the presence and absence of NO production (using inhibitors of NO synthases), superoxide bioavailability/oxidative stress (using antioxidant compounds or inhibitors of oxidant enzymes), or the treatment compound itself (Lesniewski *et al.*, 2011; Fleenor *et al.*, 2012). Biochemical characterization can be performed on vascular tissue from the same animals, with or without further *ex vivo* treatments. Similarly, in human subjects, local arterial infusion of NO synthase inhibitors, antioxidant compounds (vitamin C) and other agents can be used to 'pharmaco-dissect' the mechanisms influencing vascular function, and endothelial cells from arteries or veins can be obtained for further treatment and biochemical analysis (Shenouda *et al.*, 2011; Jablonski *et al.*, 2013; Kaplon *et al.*, 2013). Moreover, plasma, whole blood, and circulating blood cells can be assessed for clues regarding the molecular events involved using either conventional or newer high-throughput analyses. Finally, complementary cell culture experiments involving genetic and molecular manipulation of pathways of interest can be performed to provide more direct cause and effect evidence for the role of particular processes in the functional changes observed (LaRocca *et al.*, 2012; Shenouda *et al.*, 2011).

Integrative model

Using a combination of the translational approaches described above and highlighted in Fig. 3 and 4, we have developed an *integrative model* for studying the effects of various factors on physiological function (e.g. ageing), the effects of treatments to improve function, and the underlying mechanisms involved. When data in humans are not available to support an initial hypothesis, we perform preclinical studies in mice *using assessments of function that are directly translatable to humans*. Whereas a pilot study to obtain preliminary data in human subjects might take multiple years given present regulatory approval procedures, this can be done within a matter of months and at a fraction of the expense in mice. These preclinical studies also can help to guide safety, dosing and study design components for a first trial in human subjects, and may provide insight into mechanisms of action, for which protocols and measurements can be integrated into the planning for the clinical trial.

Based on these preclinical results, an initial 'pilot' trial can be conducted in healthy adults

with the physiological dysfunction of interest (vascular dysfunction, insulin resistance, impaired exercise capacity or motor function, etc.) to assess both safety and efficacy of the proposed intervention (Fig. 3). This initial study can provide preliminary results from which to determine the number of subjects needed to achieve statistical power in subsequent studies, and may offer early insight into mechanisms of action. A larger trial can then be conducted and, if the results are confirmed, an experimental basis can be created for a multi-centre clinical trial studying high-risk adults or patients with diagnosed clinical disease. Using preliminary data from each of these steps, grant applications can be developed in parallel with this investigative model.

Several alternative approaches exist. For example, the process may begin with cell culture experiments involving screening of compounds aimed at a particular target pathway, leading to testing in animal models, and so forth, as is common in the development of pharmaceuticals (Collis, 2013). In a different context, if preclinical studies are not possible and the intervention appears safe, initial evidence supporting an effect in humans might be obtained using acute administration or short-term treatment combined with a crossover design (subjects serving as their own controls) rather than using a longer treatment period. Of course, an absence of treatment effect with acute/short-term approaches could be due to insufficient treatment duration, requiring conducting the longer intervention trial you sought to avoid in the first place! Finally, in some cases, preliminary evidence supporting an intervention trial can be obtained from cross-sectional comparisons of function in groups of humans who chronically differ in the factor of interest (physical activity, dietary sodium intake, nutraceutical or pharmaceutical use, etc.).

Conclusions and challenges

Translational physiology offers new opportunities for studying function from molecular events to populations of humans, with direct relevance to clinical practice and public health. Translational approaches allow important questions to be answered more completely, and offer a potential funding advantage in the present environment in which peer reviewers are being asked to weigh the biomedical significance of the proposed work in order to differentiate among many meritorious applications. Although greater implementation of translational strategies in physiology will require overcoming numerous challenges (Seals, 2013), such efforts hold considerable promise for increasing the societal impact of our science and our competitiveness for extramural grant support.

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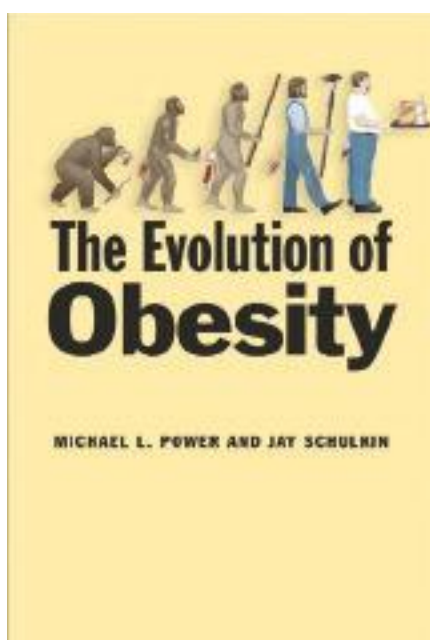
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Book review:

Evolution of Obesity Michael L Power and Jay Schulkin

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Southampton Solent University, UK



Johns Hopkins University Press

ISBN: 978-0801892622

It is becoming increasingly hard to shy away from the presence of obesity in today's society. In direct contrast to the on-going search for a 'magic bullet' cure, Power and Schulkin present a powerful reminder concerning the true complexity of the problem in hand. Providing a comprehensive overview of the evolutionary factors that predispose our nutritional and physical activity behaviours, Power and Schulkin form a well-constructed discussion, of interest to both the neophyte and the experienced academic reader alike. With copious references for the enthusiastic reader to follow up on, this one-off book focuses on a systems approach, integrating numerous levels of biology into a comprehensible whole.

The book is highly successful in its attempt to unpick and review the potential root causes of the obesity epidemic, suggesting a mismatch between our evolutionary biology and the modern-day society in which we exist. The first half of the book progressively guides the reader through specific aspects of our evolutionary history as they pertain to our biology. Setting the reader up suitably, the second half of the book explores the ways in which the modern day environment interacts with our evolved biology, and how this could potentially leave us susceptible to sustained weight gain and consequently obesity. Are the selective adaptations, which have previously dictated our success as a species, now working against us and threatening our future success? Power and Schulkin cleverly suggest: 'it is not surprising that many people get fat in this new environment; it is perhaps more surprising that many people remain lean.'

The Evolution of Obesity was a relaxing, informative and extremely easy to read book. The delivery of complex material and academic rigor is undoubtedly central to the book's success, made even more impressive by doing this without overwhelming or boring the reader. Occasionally repetitive in its message, overemphasizing points in places, there is little confusion regarding the take-home messages from each chapter. It equips the reader with a useful up-to-date context and background, upon which future work in this area can be framed. I would fully recommend this text to all academics and applied practitioners working in the area of public health, physiology and medical care. Though generally academic in its approach, *The Evolution of Obesity* is an enjoyable read from which everyone can obtain important information. Attributing the present-day obesity epidemic to a wide range of factors Power and Schulkin make little attempt to propose potential solutions to the well discussed problem. Debate around this area would undoubtedly make for fascinating reading in a follow-up book.

Obituary:

Olga Hudlická 1926 – 2014



Professor Hudlická, known to many simply as Olga, died unexpectedly after a fall. She was a member of The Physiological Society since 1972, and one of the premier vascular physiologists of the twentieth/twenty-first century. She had a remarkable life.

Olga was born in a small town in Czechoslovakia. Despite wartime occupation she completed her schooling, and afterwards entered Charles University (Prague). After her MD she joined the distinguished muscle physiologist Ernest Gutmann at the Czech Academy of Sciences, gaining a PhD in 1954. Her interest in the control of muscle blood flow became a passion for the rest of her research life. Drawing on her medical training, she used her impressive breadth of knowledge to gain unerring insights into microvascular physiology. A major contribution was in understanding the local mechanisms regulating growth of capillaries in skeletal and cardiac muscle, showing that mechanical factors (especially increased shear stress) in conjunction with growth factors play a powerful role in initiating angiogenesis.

This process is fundamental to muscle performance following endurance training. She saw with clarity how this could be applied to different clinical situations. Based on *in vivo* ischaemic models and electrical stimulation of muscles, she promoted therapeutic approaches to ameliorate peripheral vascular disease. This

has proved of great benefit to patients with intermittent claudication, and also in other cases of poor muscle blood flow (e.g. heart failure).

Her outstanding early work in Prague led to her being elected Honorary Secretary of the Czechoslovakian Physiological Society (1960–1969). Her international reputation resulted in invitations to work at the Karolinska Institute (Stockholm, 1960), and Duke Medical Center (USA, 1964 and 1968).

For many years she and her husband, a physician at the main hospital in Prague, were subject to censorship and political surveillance by secret police. Hope for change with the liberalising reforms of Alexander Dubček in 1967 was soon quashed by a Warsaw Pact invasion with tanks and half a million troops. So in 1968 Olga and her family escaped and managed by various routes to reach Frankfurt in Germany, and eventually Birmingham in the UK at the invitation of Sidney Hilton, head of Physiology at the Medical School. Here Olga was reunited with Gerta Vrbová with whom she had worked in Prague, and another good friend, Andrzej Zbrozyna, who had left Poland in the early 1960s. She remained there until her retirement in 1993, and continued to work as Professor Emeritus. She had an intense work ethic believing that the best science is done by those who tackle problems in the lab.

Olga was a keen supporter of the physiological community, and played important roles in the British Microcirculation Society (Honorary Secretary 1985–1992; President 1996–1999). She published over 200 papers, chapters and reviews (the last published in 2011); an original monograph, *Muscle Blood Flow*, appeared in 1973, the highly influential 'Angiogenesis' in 1986, and *Application of Muscle/Nerve stimulation in Health and Disease* in 2008. Her influence on the field was recognised as Visiting Professor at Frankfurt/Main, California/Davis, and Caracas (Venezuela). Prestigious awards included the Annual Review Lecture (The Physiological Society, 1990), Zweifach Award and gold medal (USA Microcirculatory Society, 1996), President's Lecture (American College of

Sports Medicine, 1998), and Malpighi Award (European Society for Microcirculation, 2008).

Olga was extremely proud to join the liberal UK scientific tradition, and British science has clearly benefited enormously from her as with many other émigrés. She valued friends and was prepared to fight against injustice. In the last 10 years she became increasingly alarmed by the rise of autocracy in our universities that, tellingly, she likened to the totalitarian system from which she had fled in 1968. In 2004 she published an impassioned article in *Physiology News* lamenting the disappearance of the Department of Physiology in Birmingham, which she had grown to love. More recently, she devoted considerable energy to a campaign, which received vigorous support from the international scientific community, for reinstatement of a colleague who had been summarily dismissed for apparent 'gross misconduct'. Her actions were vindicated when an Employment Tribunal dismissed the University's case; she was pleased that Western democracy was not altogether corrupted!

In addition to an intense work focus, she had a considerable knowledge of classical music, art and literature, loved skiing and walking, all of which she enjoyed with her husband, a busy GP who predeceased her. Olga Hudlická was a remarkable person who will be much missed. She had an enquiring mind, always curious with a never-ending thirst for knowledge. Above all she was principled, honest, courageous, generous, loyal and supportive of others. She was much loved by her children and grandchildren, who she adored. She is survived by her daughter, also a scientist, and her son, a neurologist in Washington DC, a granddaughter and two grandsons.

*John Coote
& Stuart Egginton*

*A version of this obituary appeared in
The Guardian in July 2014*

Obituary:

Abraham Guz 1929 – 2014



Abe Guz, beloved husband of Nita, father of Deborah, Gabrielle and Stephanie and grandfather to their nine children, died on April 11, 2014 aged 84. Abe left Grocer's Company School, Hackney in 1947 to study medicine at Charing Cross Medical School; he was a prize student at both institutions. We see the first evidence of Abe as a physiologist with a 1953 publication in BMJ on 'Noradrenaline in Cardiac Infarction' at the time of his first House appointment at Charing Cross Hospital. This was followed by national service as a medical officer in Germany where he achieved the rank of Acting Major.

On leaving the Army in 1955, Abe took a position at the Postgraduate Medical School/ Hammersmith Hospital alongside contemporaries and renowned future respiratory physiologists John West and Moran Campbell. Abe gained a travel fellowship to Harvard (Beth Israel) Medical School and in a 1960 publication with his mentor Al Freedberg and George Kurland found support for the existence of 'a vasodilator metabolite... of very short half-life' explaining 'the failure of others to detect such a substance in coronary venous blood'. This was a full 27 years before the identification of nitric oxide as the potent EDRF. In 1959 he transitioned to the newly formed Cardiovascular Research Institute in

San Francisco under the mentorship of Julius Comroe. Here he established life-long friendships with the likes of John Widdicombe, Karl Wasserman, John Severinghaus and John and Hazel Coleridge, and began a productive research collaboration in cardiovascular physiology with Julien Hoffman, who he had first met at Hammersmith.

In 1961, Abe returned to the Charing Cross as Assistant Lecturer in the inaugural academic Department of Medicine headed by Hugh de Wardener. Together with Mark Noble and Di Trenchard, Abe continued his cardiovascular studies and thanks to Comroe's influence, extended his research into the role of vagal pulmonary receptors on respiratory control and sensations. With help from John Widdicombe, plus a series of visiting scholars and practicing clinicians at the Charing Cross, Abe's team published a series of definitive (and sometimes heroic) vagal blockade studies in conscious and anaesthetised humans and experimental animals to greatly refine our understanding of the significance of Hering-Breuer reflexes in respiratory rhythmogenesis.

I joined Abe's group in 1977 and he turned my attention to the enigma of dyspnoegenesis (as he called it), another Comroe influence. At the time, physiologists were trying to crack this nut using classical psychophysics to define the input/sensory characteristics of a range of quantifiable respiratory perceptions. Abe saw no reason why we shouldn't measure dyspnoea directly using psychometrics, widespread in the assessment of clinical symptoms, notably pain; we settled on the Visual Analogue Scale following the lead of Edinburgh psychiatrist RCB Aitken. Psychometric assessment of dyspnoea is now widespread in Cardiorespiratory and Palliative Medicine and Abe's contribution is justly commemorated by the 'Abe Guz Lecture' at the annual congress of the Association of Palliative Medicine.

Abe succeeded de Wardener as Head of Department of Medicine in 1982 and during his tenure (until 1994) it became one of the

UK's top research units for Cardiorespiratory Physiology and Medicine. The initiatives were numerous and varied but physiology continued to be his passion. His ability to identify the changing landscapes in research, led to the setting up of one of the UK's first sleep labs and the identification of sleep-related upper airway muscle dysfunction in the pathophysiology of obstructive sleep apnoea. In the early 90's he established successful collaborations with teams at the Hammersmith and Institute of Neurology, to utilise emerging brain imaging techniques in better defining the neural basis of human respiratory control and sensation.

On retirement, Abe became Emeritus Professor and continued to inspire and advise junior colleagues and students with his drive and encyclopaedic knowledge of medical research, well into the 2000s. His ability to ask the crucial question and then identify the person/group/technology that could help get the answer was extraordinary. His 300+ peer-reviewed publications are co-authored by hundreds of research collaborators across a wide range of specialities and thanks to him many have gone on to occupy senior positions in medicine and academia. Despite his prodigious work ethic and frequent 80 hour working weeks, Abe managed to find time to be both an accomplished violinist and scholar of Jewish history... although he never did quite get the hang of driving a motor vehicle. He will be greatly missed and fondly remembered.

Lewis Adams

Obituary:

Syogoro Nishi 1929 – 2014



Syogoro Nishi was born on 22 March 1929 in Fukuoka, Japan. He died there on 13 February 2014. After graduating from Kurume University Medical School, Nishi undertook a PhD in physiology, before accepting a Fulbright Scholarship to the United States. There he joined his senior colleague from Kurume, Kyoze Koketsu, who had learned the intracellular microelectrode technique from Ralph Gerard in Chicago. Their first target with these glass electrodes was the small intrafusal muscle fibres, innervated by γ -motoneurons and setting the tone of the stretch receptors.

After three initial years in the United States, Nishi returned to the Physiology Department at Kurume. Then from 1966 to 1975 he directed the Neurophysiology Laboratory, Department of Pharmacology and Therapeutics, of Loyola University's Stritch School of Medicine in Maywood, Illinois. In the late 1950s, the Koketsu and Nishi partnership made the first detailed intracellular recordings from sympathetic ganglia and from primary afferent neurons of the spinal ganglia in frogs: over the next decade or so they elucidated the role of

calcium ions in the action potential, deduced the repertoire of ionic conductance present in the cells, and determined the ionic mechanisms of the synaptic inputs. Nishi particularly contributed to our understanding of the mechanisms underlying the slower synaptic potentials (slow EPSP, slow IPSP, late slow EPSP) resulting from repetitive stimulation of the preganglionic nerves. He demonstrated that noradrenaline inhibited the fast EPSP by directly inhibiting the release of acetylcholine (with Christ and Dun). He pioneered the methods for recording from the tiny ganglia of the enteric nervous system, distinguishing between the admixed efferent and afferent neurons of the myenteric plexus (with North). He showed that γ -aminobutyric acid depolarized primary afferent neurons, and by inference their terminals in the spinal cord, by increasing the membrane chloride conductance (with Gallagher and Karczmar). Throughout this period, his reputation developed for technical mastery, and for publications of unusual completeness and authority.

His career continued in Kurume from 1975, and he served in due course as Head of Physiology, and Dean of the Medical School. He strengthened his contributions to our understanding of enteric ganglia and afferent neurons (with Higashi, Katayama and Mihara) but also adopted the brain slice methodology to bring similar approaches to the central nervous system. He described the fundamental properties of neurons in particular nuclei, and their synaptic inputs (dorsal raphe, nucleus accumbens, anterior cingulate cortex, central amygdala and hippocampus, with Tanaka, Higashi, Uchimura and Inokuchi). However, his major impact during this period remained the autonomic nervous system. With Yoshimura and Polosa, he determined the membrane properties of preganglionic sympathetic neurons in the spinal cord, showing how an unusually long afterhyperpolarization determined the discharge patterns of these neurons.

This work was recognised by election to Honorary Membership of The Physiological Society in 1999, and by an award by the Emperor of Japan in 2008 for his services to science and education, of the 'Order of the Sacred Treasure, Gold Rays with Neck Ribbon'.

Syogoro Nishi asked scientific questions that required not only remarkable technical skill but also unusual calm perseverance. The beautiful results very often arrived late at night. He was well suited by temperament to this approach, for his prowess was matched by his humility. The world is richer not only because we know more about autonomic neurons, but because many of us have been touched and inspired by the company of a man who seemed to bring his personal kindness into the laboratory with him.

*R Alan North
& Alexander Karczmar*

Notices and full obituaries can be found on The Society website at www.physoc.org/obituary-notices

Experimental Physiology

The Physiology and Pathophysiology of Obesity Themed Issue



The September issue of *Experimental Physiology* is a Themed Issue entitled The Physiology and Pathophysiology of Obesity. It contains Symposium Reports from the Society's Topic Meeting plus high quality original, peer-reviewed articles from active researchers in this field.

Publication of the issue is on 10 September to coincide with start of The Physiology of Obesity topic meeting and is freely accessible to all meeting delegates. A Virtual issue of obesity related articles previously published in *Experimental Physiology* is also being published at this time.

2013 Early Career Author's prize winners



Results of the 4th Annual *Experimental Physiology* Early Career Author's prize were announced at Physiology 2014 Meeting. The winner was Nathan Bracey for the article 'The Nlrp3 inflammasome promotes myocardial dysfunction in structural cardiomyopathy through interleukin-1 β ' (Bracey N A, Beck P L, Muruve D A, Hirota S A, Guo J, Jabagi H, Wright J R Jr, Macdonald J A, Lees-Miller J P, Roach D, Semeniuk L M & Duff H J (2013) *Exp Physiol* **98**, 462–472).



The runner up was Fan Ye for the article 'Overexpression of insulin-like growth factor-1 attenuates skeletal muscle damage and accelerates muscle regeneration and functional recovery after disuse' (Ye F, Mathur S, Liu M, Borst S E, Walter G A, Sweeney H L & Vandenborne K (2013) *Exp Physiol* **98**, 1038–1052).

New Editor

We are pleased to announce the appointment of Carolyn Barrett from Auckland NZ who will handle papers in the Autonomic neuroscience and cardiovascular control areas.



The Journal of Physiology

New Senior Editors to boost Muscle research

We are delighted to announce that three new Senior Editors have joined *The Journal of Physiology* team this July.

- Don Bers, UC Davis, USA, whose research focuses on the cellular and molecular factors involved in the control of cardiac muscle contraction.
- Mike Hogan, UCSD, USA, who researches muscle respiration, metabolism, performance and fatigue.
- Scott Powers, University of Florida, USA, who investigates the effects of muscular exercise and inactivity on both cardiac and skeletal muscle.

We would also like to thank Glenn Toney and Håkan Westerblad, who are retiring from their position on The Board this year, for all their hard work and commitment to *The Journal* over the years.

New Reviewing Editors

The Journal of Physiology would like to welcome the following new Reviewing Editors who started their role on *The Journal* in July 2014:

- | | |
|-------------------|--------------------|
| • Bruno Allard | • Matt Nolan |
| • Andrew Allen | • Jochen Roeper |
| • Diego Contreras | • Michael Shattock |
| • Ann Goodchild | • Jesper Sjöström |
| • Dino Giussani | • Richard Wise |
| • Bjorn Knollmann | |

Ageing and Degeneration: A physiological perspective



The Journal of Physiology is pleased to announce that it will be publishing two special issues on the topic of Ageing and Degeneration, to tie in with The Physiological Society's 'Understanding Ageing' year in 2015. One issue will be focused on neuroscience (classic neurodegenerative diseases), and the other issue will cover all other areas of physiology, with an emphasis on the effects of age on exercise and cardiac performance, muscle degeneration and vascular change.

The last word

Otto Hutter turns 90

One of the Society's longest-standing and most distinguished members, Otto Hutter, celebrated his 90th birthday earlier this year. He was elected a member in 1953 and an Honorary Member in 1991. Otto, who now lives near Bournemouth, enjoyed what was mainly a large family gathering, surrounded by children, grandchildren and great-grandchildren and close friends. But he and Yvonne had also invited his 'young student', Denis Noble, as well as Tom Sears, a friend since the 1940s as they met at (the then) Burroughs & Wellcome labs in Beckenham, Kent, and me, one of his former Glasgow staff.

A particular pleasure was witnessing the amazement and interest of some of the younger members of Clan Hutter as they listened to Denis explaining to the gathering something of why their grandfather is held in such esteem in the community of physiologists. For all those who wonder at it, Otto's vivacity is better understood when we remember that, as a 29th February child, he is actually still only 22½. Many happy returns.

David Miller



Denis Noble and Otto Hutter