

# PN

Physiology  
News

Issue 125/ Spring 2022



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of the sunshine vitamin*

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edition of *Physiology News*

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# Processing and Modulation of Sensory Signals: From the Periphery to the Cortex

Early registration  
deadline  
**30 April 2022**



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- Expand your knowledge of sensory physiology with our international panel of speakers
- Receive feedback on your work from world-leading experts

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 **The  
Physiological  
Society**

## Welcome to the first issue of *Physiology News* in 2022



### *Dr Keith Siew*

Scientific Editor,  
*Physiology News*

To both our new and returning readers, welcome to the first issue of *Physiology News* for 2022. As we enter yet another tumultuous year on the rollercoaster that is the 2020s, I want to take this opportunity to write a little more candidly.

First, I want to publicly express my sincerest of thanks to my dear colleague and friend Julia Turan, who was the Managing Editor of *Physiology News* for my tenure thus far as Scientific Editor. It was a dream to work with you, and you brought so much positive change to *Physiology News*, which we will be forever grateful for and couldn't have been done without you. Your passion for science communication and Diversity & Inclusivity issues were inspirational and will leave a lasting impression on all that we do going forward. I know I and the rest of the Editorial Board will very much miss you and we wish you every success in your future endeavours.

Since it has been a while since I've written an editorial myself, I want to send my belated thanks also to those who stepped down from the Editorial Board, Karen Doyle and Angus Brown, for their invaluable contributions over the past number of years. Also a

big welcome to our new Editorial Board members Wendy Hempstock, who joins us all the way from the land of the rising sun, and Alex Carswell, who is a little closer to home, in beautiful Norwich. In this issue, Alex writes on the fascinating history of vitamin D (p.16) and is joined by articles on the use of stems cells in tissue engineering for regenerative medicine (p.24), an immensely useful article on the pharmacology tools that may be useful to physiologists (p.28), and also an interesting look into the moment that the calcium theory of phototransduction fell from grace (p.20).

Later this year we also hope to be bringing you some exciting new content with special themed issues on sensory physiology to coincide with a joint meeting of The Physiological Society and Sainsbury Wellcome Centre ([physoc.org/sensory-signals](https://physoc.org/sensory-signals)) taking place in London in June. As well as a dedicated issue on the role of physiological science in the response to climate change, which will coincide with the Europhysiology 2022 meeting held in Copenhagen in September ([europhysiology2022.org](https://europhysiology2022.org)).

Lastly, I am sending my heartfelt support to my Ukrainian friends and colleagues, as well as your family and peoples, during this unjust war of invasion being waged against your beautiful country by Putin. Like many, I am glued to the news coverage, horrified by what I see and hear. In particular, I was caught emotionally off guard by a Sky News

reporter interviewing two young women in Kyiv, a biochemistry postgraduate student and a schoolteacher. The comforts and routine of daily life in the lab or classroom only a few days prior torn asunder as they were now compelled to enlist in civilian resistance forces, learning to shoot rifles and make petrol bombs to fight for freedom. I couldn't help but put myself in their shoes, and think of my own students, and wonder whether we would have had the courage to do the same under similar circumstances.

I was extremely heartened to see that The Society has made a statement of solidarity and I want to also amplify the messages of support and draw attention to The Society's Support and Inclusion fund, which can provide £1,000 to support those who need it, for instance with housing/living costs ([physoc.org/support-and-inclusion-fund](https://physoc.org/support-and-inclusion-fund)). I also am inspired by EMBO, which is providing a list of life scientists across Europe and beyond offering to host Ukrainian researchers in their labs ([embo.org/solidarity-with-ukraine/](https://embo.org/solidarity-with-ukraine/)), and also by #ScienceForUkraine ([twitter.com/Sci\\_for\\_Ukraine](https://twitter.com/Sci_for_Ukraine)) where the scientific community is rallying to provide support for our Ukrainian colleagues impacted by the invasion. I urge all of you to check out these resources and lend your support if you have the means to do so!

I hope you, and all your families and friends, remain safe and well during these most uncertain of times.

# Ireland at the heart of physiology and The Society



*Professor David Paterson*

President,  
The Physiological Society

All of us in The Physiological Society stand in solidarity with our friends and colleagues in Ukraine. We are deeply shocked at the barbaric unprovoked invasion of Ukraine. Physiologists are a global family and we have watched in horror at the scenes of bloodshed unfolding. Ukraine has a proud history of physiological research and The Society is proud to count Ukrainian scientists among our members. For more information about The Society's response, please visit our website.

## Ireland and The Society

Throughout our history, Irish physiologists have been at the heart of The Physiological Society. Irish physiologist Gerald Francis Yeo was among the 19 men who met in John Burdon Sanderson's house on 31 March 1876 and agreed to form The Society as 'an association of physiologists for mutual benefit and protection'. He also served as one of The Society's first secretaries (O'Connor, 1988).

As the establishment of The Society pre-dates the formation of the Republic of Ireland, it has continued to be the home society for British and Irish physiologists. Irish physiologists have made significant contributions to The Society itself and research within the discipline.

The discipline of physiology is highly visible in Irish higher education institutions, with many featuring named physiology departments. Physiology continues to be a popular choice for students at undergraduate and postgraduate level thanks to the high-quality teaching and research programmes on offer.

As a result of strong physiology research programmes at Irish institutions, Irish physiologists are well represented in our

discipline's publications. Twenty-seven papers published in *Experimental Physiology* and *The Journal of Physiology* since 2020 have corresponding authors from Irish institutions. One of those authors is a new Society Trustee, Professor Paul McLoughlin. Paul is our Chair of the Publications Committee as well as Professor of Physiology and Head of the Biomedical Sciences Section at University College Dublin.

Professor Áine Kelly has also recently become a Trustee and is Professor in Physiology at Trinity College Dublin. Áine was elected to the Board specifically to help Trustees navigate the scientific, higher education and policy landscape in the Republic of Ireland.

I look forward to working alongside both Paul and Áine – and members across Ireland – to increase our representation of the issues that matter to Irish institutions.

## Irish policy priorities

The future of an ageing society is a significant scientific and public policy challenge facing countries across the world, for which physiology research is vital to addressing. In Ireland, a projected shift in the demographic composition of the population means it will have one of the most rapidly ageing populations in the European Union over the coming decades.

In September 2021, the Irish Minister for Finance, Paschal Donohoe TD, published *Population Ageing and the Public Finances in Ireland*. The report found that the old-age dependency ratio in Ireland – the number of retirees as a fraction of the number of workers – is set to nearly double over the next 30 years, from 24% at present to 47% by 2050. Associated age-related expenditure is set to be €17 billion higher in 2050, in today's terms, than in 2019. The report also found that in a hypothetical scenario in which there were no further policy responses, the fiscal costs associated with population ageing would add around 20 percentage points to the debt-to-gross national income ratio by 2050 (Government of Ireland, 2021). This clearly puts significant pressure on public finances as well as a coordinated public health response to ensure older people in Ireland are empowered to live well in older age.

Healthy ageing is a policy priority for The Society, and we continue to successfully highlight the vital role of physiology research in addressing the challenges presented by the ageing population. While our work so far has

engaged UK policymakers, in 2022 we will increase our focus on the landscape in Ireland. Similarly, later this year we will work with Irish members on a campaign to promote the invaluable contribution that physiology research and teaching makes to Ireland's economy and society.

A lesson from COVID-19 has been that, throughout the world, the best defence against unforeseen events is a robust, diverse science base we can call on. However, funding for research and development (R&D) in Ireland is consistently low, with the latest figures showing that Irish R&D spending accounts for only around 1.15% of GDP. In comparison, the latest figures for the UK show R&D spending is at 1.74% and the UK Government is committed to reaching 2.4% of GDP. The Society will be working with members in Ireland to raise our concerns about Irish R&D funding levels with policymakers.

## Events and conferences

In addition to our planned policy focus, The Society is looking forward to an expanded programme of events and conferences at Irish institutions. For example, in June we will be celebrating Gerald Francis Yeo's work by unveiling one of The Society's blue plaques at Trinity College Dublin to honour his legacy and contributions to physiology. This will be preceded by the unveiling of another of The Society's blue plaques at Queen's University Belfast to commemorate the life and work of Henry Barcroft. The Society will also be supporting the centenary celebrations at Trinity College Dublin 'Physiology@100: Past, Present & Future' by awarding the Paton Prize Lecture – which aims to promote interest in the history of scientific experiments and ideas.

Irish physiologists continue to make a significant contribution to the health of The Society and the discipline. I look forward to meeting more Irish members in 2022 and sharing their successes with you.

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# The vital role of physiologists in tackling the long-term consequences of COVID-19

*Daniel Burdass*

Chief Executive,  
The Physiological Society

As I write my first "Chief Executive's View" of 2022, I feel fortunate to be doing so from our headquarters in London. I felt that back-to-school excitement and buzz to be meeting face to face with colleagues in the office when the restrictions were again lifted in January.

While the COVID-19 pandemic is still very much a feature of our daily lives and facemasks continue to be the norm, I hope that meeting in person will be able to continue. Both for staff, for our members and the wider community of physiologists as we create opportunities for in-person collaboration and networking – to raise the visibility of physiology through an inclusive approach for a sustainable future.

As we enter the third year of living with COVID-19, I thought I would reflect on what has gone before and think of the year to come with its many opportunities and, no doubt, challenges for both physiology and physiologists.

Since the emergence of the novel virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, it has spread across the globe, having a profound effect on our health and lives. Globally, as of 28 January 2022, the World Health Organization reports there have been 364,191,494 confirmed cases, including 5,631,457 deaths (WHO, 2022).

When Coronavirus Disease 2019 (COVID-19) was first documented it was initially assumed to be a respiratory disease and classification was based around pneumonia severity, breathlessness, and low oxygen levels. Doctors and scientists including physiologists worked to try and understand this completely new disease and how to treat it. However, reports came in describing, mainly in severe cases, that in addition to the virus affecting the lungs it was also affecting multiple organs such as heart, liver and kidney, as well as the haematological and nervous systems (Mokhtari *et al.*, 2020).

The Society quickly formed a COVID-19 advisory panel and launched our "Questions from the Frontline" initiative, which sought

to provide physiological insight to clinicians dealing with patients by providing an evolving understanding of the physiological and pathophysiological mechanisms underpinning this disease.

We followed this up with "COVID-19: Lessons from the Frontline". Working with the Intensive Care Society, the conference shared current knowledge and thinking across many physiological systems, showcased the symbiotic relationship between physiology and clinical care and helped set the agenda for research to identify future treatments and therapies.

Most people who have COVID-19 recover completely within a few weeks. But some have long-term problems recovering from the infection – even those who had mild versions of the disease. The term "long COVID" was coined for post-COVID conditions by patients (Perego *et al.*, 2020); other terms have also been used, such as long haul COVID, post-acute COVID-19 and chronic COVID.

The guideline scope published on 30 October 2020 by health watchdog the National Institute for Health and Care Excellence (NICE, 2020), defines long COVID as signs and symptoms that develop during or following an infection consistent with COVID-19, which continue for more than 12 weeks and are not explained by an alternative diagnosis. The definition says the condition usually presents with clusters of symptoms, often overlapping, which may change over time and can affect any system within the body. It also notes that many people with post-COVID-19 syndrome can experience generalised pain, fatigue, persisting elevated temperature and psychiatric problems. But there is no agreed-upon definition.

In a BMJ Opinion piece by Professor Paul Garner seven weeks into his journey he described his rollercoaster of ill health, extreme emotions, and utter exhaustion following COVID-19.

*The illness went on and on. The symptoms changed, it was like an advent calendar, every day there was a surprise, something new. A muggy head; acutely painful calf; upset stomach; tinnitus; pins and needles; aching all over; breathlessness; dizziness; arthritis in my hands; weird sensation in the skin with synthetic materials. Gentle exercise or walking made me worse—I would feel absolutely dreadful the next day.*

The Office for National Statistics (ONS) estimates about 1.3 million people in the UK were experiencing self-reported long COVID (symptoms persisting for more than four weeks after the first suspected COVID-19 infection that were not explained by something else) as of 6 December 2021 (ONS, 2022). It is clearly a public health concern affecting people's ability to resume normal life and their capacity to work.

The Society ran an online conference in February 2022 – Long COVID: Mechanisms, Risk Factors, and Recovery – which reviewed the challenges of understanding the pathophysiological changes following COVID-19 infection. It brought together physiologists and clinicians, so we can better understand the underlying mechanisms and identify potential therapies. The conference report can be found on p.36.

Tedros Adhanom Ghebreyesus, WHO's Director-General, has called on countries to prioritise recognition, rehabilitation, and research for the long-term consequences of COVID-19, as well as collection of data for long COVID (Ghebreyesus, 2020). As new variants of the virus occur, physiology and physiologists will be at the forefront of this search for answers.

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## Reports of The Society's recent committee meetings

*The purpose of these short updates is to keep you informed about the work of our committees. The following summaries detail the meetings of the past few months.*

### Board of Trustees

#### September 2021

Following a successful Member Roadshow and unveiling of the Blue Plaque to Sir Charles Sherrington at the University of Liverpool, Trustees met in person in Liverpool on 30 September 2021 for the third Board meeting of the year.

The President welcomed the two incoming General Trustees in attendance: Áine Kelly from Trinity College Dublin and Heidi de Wet from the University of Oxford.

The President thanked Elizabeth Sheader and David Eisner for hosting the successful Member Roadshow and A.V. Hill Blue Plaque unveiling at the University of Manchester. He also observed that the Sherrington plaque unveiling had gone well at the University of Liverpool and noted the Vice Chancellor Professor Dame Janet Beer had not only unveiled the plaque but had also attended the Roadshow and dinner. The President noted that the Roadshows provided an excellent opportunity to reconnect with institutional leadership in support of the charitable aims of The Society. The Chief Executive added that the Roadshows also offered a connection to institutions within a region.

The President summarised the upcoming 2021 plaque unveilings as including Mary Pickford at the University of Edinburgh, Mabel Fitzgerald at the University of Oxford, Winifred Cullis at the Royal Free Hospital and Lord Adrian at the University of Cambridge. The President confirmed that the physiologist and NASA astronaut Jessica Meir would be unveiling the Fitzgerald and Cullis plaques in conjunction with the President's Lecture at the Royal Society in London.

The Honorary Treasurer updated Trustees that the revised forecast (August 2021) to 31 December 2021 had resulted in an operating surplus of £0.2m before investment gains, an improvement of approximately £0.58m compared to the budget. The Honorary Treasurer confirmed that Finance Committee had approved the proposal to increase the continuity fund to cover an additional 6 months of operating costs (from 24 months to 30 months) and that a further £1.5m was transferred to increase the fund to £7.1m. This provided a substantial buffer, should it be required due to a sudden loss of income.

The Chief Executive updated Trustees that the 19 November Member Forum at the Royal Society would now have a sit-down dinner for invited guests instead of a reception with demonstrations and finger food. This was due to COVID-19 restrictions and a cap on numbers required by the Royal Society but would not impact on budget.

The Chief Executive flagged to Trustees that the COVID-19 hub on the website had now

been replaced with a COP26 hub showcasing a variety of related content and resources.

The Head of Policy and Communications delivered a presentation to Trustees entitled 'Policy Horizon Scanning & Our Response' analysing upcoming policy that would affect physiology and The Society.

The Head of Professional Development and Engagement delivered a presentation introducing the topic of Research Culture and the work done in this space since the first 2014 Nuffield Council on Bioethics Report. Top issues included short-term funding, lack of wider societal engagement, and a lack of incentive for team working.

### Finance Committee

#### September 2021

The Committee received the second quarter Management Accounts which contained figures from an August, 2021 reforecasting exercise and showed an improved operating surplus, with both income and expenditure down. The Committee also received a cash flow forecast paper, which illustrated the December Wiley publishing advance and subsequent depletion of cash reserves through the year.

The Committee agreed to support the Board's request for an external publishing consultant specialist and approved the proposal to increase the continuity fund to





cover an additional 6 months of operating costs. The Committee also approved recommendations for the improvements to the second floor and flexible working space of Hodgkin Huxley House and to put both spaces out to market.

The Committee heard a presentation from the new investment manager at Rathbone Greenbank, which included a summary of investment objectives, risk profile and ethical considerations.

## Conferences Committee

### October 2021

Professor Sue Deuchars (University of Leeds, UK) was warmly thanked for her efforts since 2017 as Chair of Conferences Committee, particularly for those during the recent difficult months of the pandemic. The Committee also recognised outgoing members, Professor Deborah Baines (St George's, University of London, UK), Professor Professor Holly Sheils (University of Manchester, UK), Dr Stefan Trapp (University College London, UK), Professor Ian Forsythe (University of Leicester, UK), Dr Mike White (University of Birmingham, UK) and Dr Llwyd Orton (Manchester Metropolitan University, UK).

There followed a robust discussion about increasing diversity in Society Prize Lecture nominations, and also the "Aspiring Black Physiologists" initiative.

The plans for 2022 conferences were discussed, with many of the meetings having been carried over from 2020 and 2021 in light of the COVID-19 pandemic. The Committee also discussed 2023 Society conferences and meetings, together with the future of the Europhysiology series of meetings.

It was hoped to select the new Theme Leads for Cardiac & Vascular Physiology, Endocrinology, Epithelia & Membrane Transport, and Human, Environmental & Exercise Physiology. The Committee shortlisted applications and asked these for more information. Professor Dan Martin (University of Plymouth, UK) was co-opted to join the Committee to represent the clinical community.

## Policy Committee

### January 2022

The inaugural meeting of the Policy Committee was held virtually, chaired by Professor Mike Tipton (University of Portsmouth, UK). Professor Tipton thanked the Committee

members for their interest in the work of the new Committee and for agreeing to participate in its discussions and outputs.

The members of the Committee introduced themselves and their policy interests.

The Committee discussed The Society's policy strategy for 2022 and received a presentation from the Head of Strategy, Policy & Communications on the wider policy landscape for physiology and R&D more broadly. The Policy Manager gave an overview of recent policy work.

The committee members expressed their thanks to the Education, Public Engagement and Policy (EPEP) Committee for their work in this area and agreed to continue the workstreams that were approved by the EPEP Committee at their last meeting.

The Committee discussed three areas of policy: a policy project focusing on the Republic of Ireland, a project looking more closely at the UK Government's stated priorities for ageing research within the *Life Sciences Vision*, and the work of the *in vivo* taskforce in 2022.

The Committee also received reports on The Society's other areas of policy focus including knowledge exchange and interdisciplinary research.

# Variability, Physiological Variability and Individual Responses: A Practical Research Workshop

26 September 2022  
London, UK

Variability is ubiquitous in physiological research, but we often choose to ignore it, hide it or remove it. This workshop will provide guidance and worked examples to help you assess and understand how to use variability in your statistical methods.



Develop your  
statistical knowledge



Discuss different  
experimental designs



Step-by-step guidance  
from experts

Submit your  
own data  
for worked  
examples



Register from 15 April: [physoc.org/variability](https://physoc.org/variability)

 The  
Physiological  
Society

# How can we develop a National Post-Pandemic Resilience Programme?

*Dr Alison Giles*

formerly Director of the Centre for Ageing Better

*Professor Paul Greenhaff*

MRC Versus Arthritis Centre for Musculoskeletal Ageing Research and NIHR Nottingham Biomedical Research Centre, University of Nottingham, UK / The Physiological Society

*Tom Addison*

Policy Manager, The Physiological Society

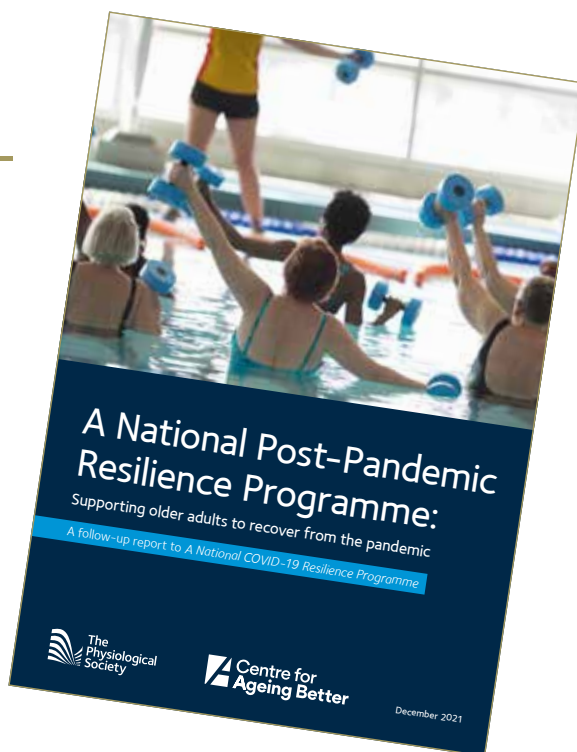
Throughout the COVID-19 pandemic, older people have been disproportionately affected by the virus. Despite an overall decline in hospital admission rates between 2020 and 2021, hospitalisations in the over-75s continue to far outnumber those in younger age groups (ONS, 2022). The risk of death from COVID-19 has remained closely correlated with age throughout the pandemic (UK Government).

Two years on from the first COVID-19 infections, the national rollout of vaccines has fundamentally changed the nature of the pandemic. Given the reductions in deaths and hospitalisations as a result of vaccines and treatments, we can now start to contemplate a post-pandemic world. As part of that, it will be essential to address the impact of COVID-19 lockdowns and restrictions on the mental and physical health of older people.

The Physiological Society and the Centre for Ageing Better brought together physiologists, nutritionists, geriatricians, physiotherapists and clinicians to discuss critical areas where the impact of the pandemic and lockdown on older people required greater consideration. The resulting report, *A National Post-Pandemic Resilience Programme: Supporting older adults to recover from the pandemic* was published in December 2021.

## Key findings

As the UK emerges from the COVID-19 pandemic, we asked YouGov to survey 2,014 older people to give us an indication of what the long-term impact of lockdowns and restrictions may be on their health. The results clearly showed that the pandemic has had a detrimental impact on physical activity levels: despite restrictions now being lifted, over a quarter of over-50s told us they are less physically active than pre-pandemic. Given the role of physical activity in maintaining health, this is a cause for real concern and it is likely that general health will have diminished as a direct consequence. This was particularly acute in the over-75s (34% of respondents) – an age group in which a loss of function is more likely to lead to a noticeable reduction in quality of life (the difference, perhaps, between being able to leave the house independently, drive a car etc.).



There was noticeable variation in the reasons behind the lack of physical activity by gender. Women were more likely to report a lack of motivation compared to men (47% compared to 39% of men), while men were more likely to report a loss of habit of exercise or socialising in person (43% compared to 41% of women).

Despite a reduction in physical activity compared to pre-lockdown in all age groups surveyed, the means by which different age ranges felt they would be motivated or encouraged to do more physical activity differed. Those aged 50–59 preferred activity monitors and tracking apps, 60–74-year-olds preferred social activity groups and those aged 75+ preferred tailored advice from a healthcare professional. This should come as no surprise given that most 50–59-year-olds will be in some form of formal work and will be faced with the same changing working practices (increased homeworking, reduction in face-to-face contact with customers and business networks) as the rest of the workforce. As our respondents moved towards and into retirement, the need for more social (and then tailored) forms of physical activity increased.

## Key recommendations

We are calling for public health agencies across the UK to launch a National Post-Pandemic Resilience Programme: a joined-up system of support to provide older people with tailored advice and guidance on how to improve health post pandemic. The aim should be to not only return older people to their pre-pandemic physical activity levels but encourage greater long-term levels of activity.

## Find out more

The Physiological Society and Centre for Ageing Better's report *A National Post-Pandemic Resilience Programme: Supporting older adults to recover from the pandemic* can be found at: [physoc.org/policy/covid19resilience](https://physoc.org/policy/covid19resilience)



Regular exercise increases physical resilience in older people.

A National Post-Pandemic Resilience Programme should include:

**A programme of physical activity to increase physical resilience in older people, particularly those with conditions that put them at higher risk of complications from a COVID infection such as obesity, type 2 diabetes, cardiovascular disease and sarcopenia.**

This programme of physical activity would be facilitated through a network of local groups to provide guidance and support. The programme will need to be designed in conjunction with exercise scientists and older people themselves. Such a programme will improve both physical and mental health.

**A specific focus on increasing physical activity of people in their 50s to prevent future frailty.**

Older people should be engaged long before they are considering retirement to support them to take steps earlier to live longer, healthier, happier lives. The 50–59 group should be provided with activity trackers and online information to give them the ability to take control of their own health, as well as partnering with employers to promote workplace health.

**“At home” physical activity options.**

Twenty-three percent of older people surveyed expressed concern about catching COVID-19 as a reason they had reduced their physical activity levels. “At home” physical activity options would help those who are not yet ready to go back to busier places to increase their activity levels in a way they feel comfortable with, and would therefore be more likely to undertake regularly.

**Clear guidance about the importance of a healthy balanced diet.**

This advice should be linked explicitly to maintaining health and the body’s resilience in later life, so that older people understand the direct link between lifestyle choices and health and resilience.

### Steps to embed behaviour change.

None of this programme’s proposed activities will work unless we can successfully re-build older adults’ confidence and support them to stay active and keep well. Therefore, we will need to be able to enlist the help of relatives, care workers and other professionals to reinforce messages around resilience in their day-to-day interactions with older people in their families or for whom they care.

### Launch event

The report was launched at an online event chaired by Dr Alison Giles and with participation from Professor Paul Greenhaff, Sue Dewhirst from NHS England, Alison Ilif from the Office for Health Improvement and Disparities (OHID) and Beth Mitchell from GreaterSport in Manchester. All the panellists provided a short overview of how their organisations are responding to the need to keep older people active in the aftermath of the pandemic. Questions from the audience focused on how to increase physical activity in different settings (such as care homes) and the physiological trial data that underpin the need to maintain function in later life. Audience members were also encouraged to share the report’s findings with their organisation and reach out to the organisations represented on the panel for more information about their work in this area.

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## Letter to the Editor

Dr Keith Siew,  
Scientific Editor, *Physiology News*.

25 November 2021

Dear Sir,

The oxyhaemoglobin dissociation curve is usually plotted on arithmetically scaled axes for partial pressure of oxygen and percentage saturation. If partial pressure is plotted on a logarithmic scale the curve becomes S shaped. This suggested that plotting the dissociation curve on log-probability paper might produce a straight line. This is the case for values of  $PO_2$  from between 10 and 100mmHg. At more extreme values the line departs from linearity. I am not sure whether such a plot of the oxyhaemoglobin dissociation curve has already appeared in the literature, a preliminary search failed to find any examples. I would be grateful to hear from other physiologists whether they have come across use of this transform to linearise the oxyhaemoglobin dissociation curve.

Professor R L Maynard CBE

## Celebrating physiologists and physiology at the Member Forum, Award Ceremony, and The President's Lecture



Dr Jessica U. Meir gave The President's Lecture



A full house for The President's Lecture at the 2021 Member Forum

At the end of 2021, we held our first day of in-person events in almost two years. The Royal Society was host to our Member Forum, followed by an Award Ceremony and The President's Lecture. These events were a true celebration of our community and the fantastic work of physiologists all around the world... and beyond. Indeed, this year, our President's Lecture "Experimenting in microgravity: Full circle for a scientist turned astronaut" was given by NASA astronaut and physiologist, Dr Jessica U. Meir.

### Member Forum: putting visibility, inclusivity, and sustainability at the heart of The Society

Every year, our Member Forum provides a great opportunity to reflect on the year gone by and to look ahead to our exciting plans. In his President's report, Professor David Paterson summarised The Society's focus: connection - referring to both the reconnection with our long-standing members, as well as looking towards the future generation of physiologists and connecting with new members.

*"We want to be seen as an inclusive and prominent society and use this position to continue to bolster the discipline."*

The Member Forum also saw updates from the Chief Executive, Dariel Burdass, a financial summary, and journal updates. Finally, it was an opportunity to thank demitting Trustees and Trustee Chairs and to welcome their successors.

### Award Ceremony and The President's Lecture: celebrating outstanding physiologists and physiology

It was fantastic to be able to recognise excellence in physiology in person at our Award Ceremony. Awards were given to our 2020 and 2021 Rob Clarke winners: undergraduates who had completed outstanding research projects and had presented at our scientific conference.

We also celebrated our new distinguished Fellow Members, and prestigious Honorary Fellows (read more about our latest Honorary Fellows on p.40).

The Award Ceremony was followed by the 2021 President's Lecture, given this year by astronaut and physiologist, Dr Jessica U. Meir. Dr Meir's talk was as informative as it was inspirational – giving a glimpse into her fascinating career, which ranged from investigating oxygen depletion in marine mammals and birds to being part of the first all-woman space walk and the physiological challenges and triumphs of time spent in microgravity.

After many months of not being able to meet face to face, it was a pleasure to be able to connect with friends and colleagues and to celebrate our worldwide community of physiologists together.



Honorary Fellows with 2021 President's Lecturer Dr Jessica U. Meir



Professor Deborah Baines receiving a Society Dog from Society President Professor David Paterson



Professor Giovanni Mann, who chaired the event, addresses the Member Forum



The Society President giving his report



Chief Executive, Darel Burdass, giving her update



Members enjoyed meeting face to face



Rob Clarke Award winners with Dr Jessica U. Meir



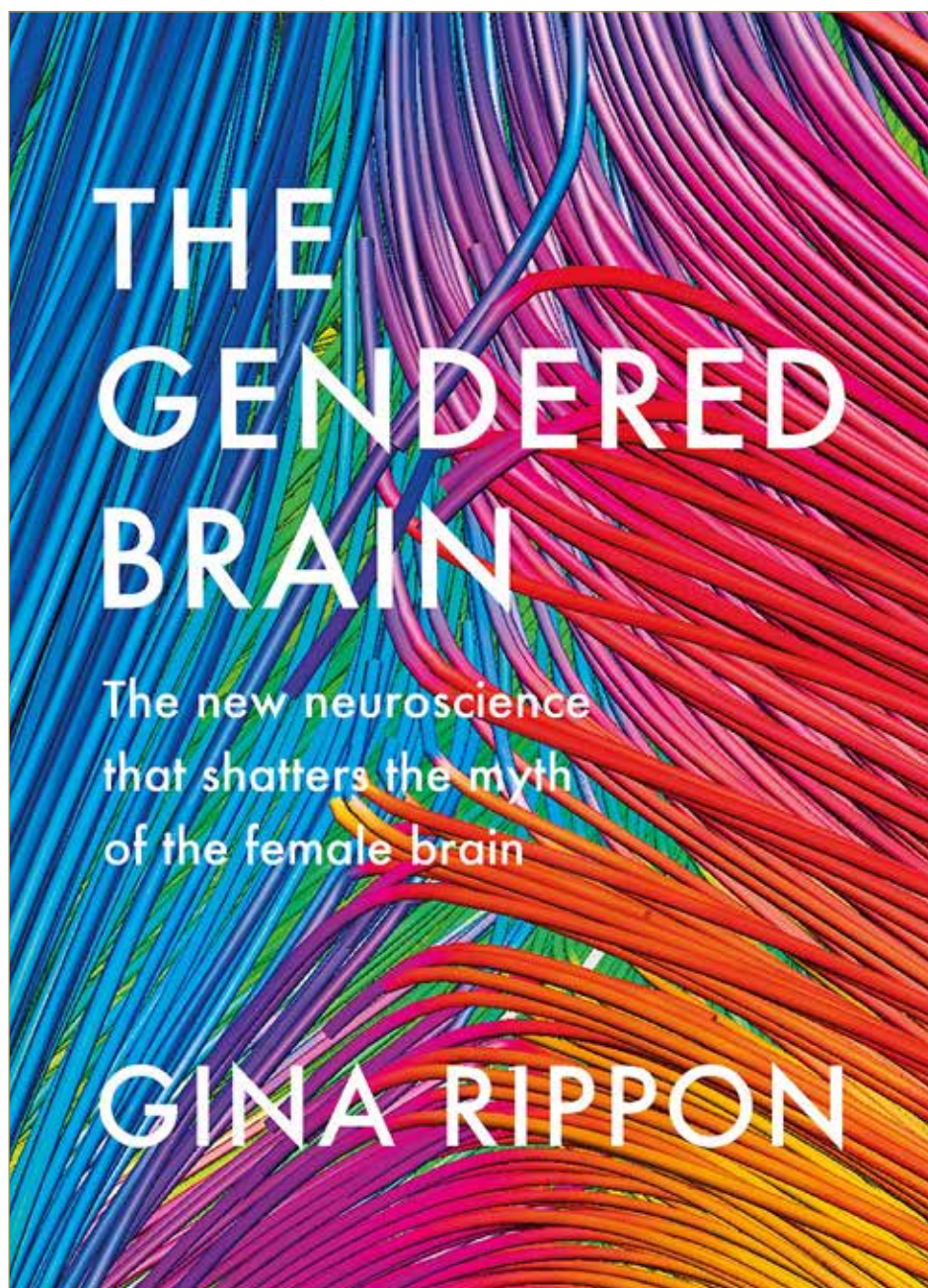
Professor Sue Deuchars receiving a Society Dog from The Society President



Networking at the champagne reception

## Book Review: The Gendered Brain: The new neuroscience that shatters the myth of the female brain

by Gina Rippon



*Dr Philip Lewis*

University Hospital of Cologne,  
Germany

According to the argument put forward by the author, my membership of the XY sex chromosome category has defined many of the gendered stimuli I will have been exposed to since birth (possibly “blue for boys” as an example but I cannot remember that far back).

Subsequent genetic, environmental and gene–environment interaction effects will then have further defined the amount and

effect of subsequent gendered stimuli in a circular fashion. This includes how others react to me and make decisions concerning me. The gendered stimuli I have been exposed to can play a role in shaping the opinions I form, decisions I make, and reactions I have. They can even play a role in my performances in various situations. In a nutshell, this is the development and effect of “unconscious bias”. Already somewhat aware of this, and taken together with my XY membership and my expectations about the book’s content, I was a bit nervous about reading/reviewing in case my review erred toward negative. I do not believe unconscious bias on my part has played a strong role in my review (of course, I cannot be sure), but it may play a role in how this review of a book with strong arguments on a controversial topic might be received. Ultimately, I have mixed feelings about the book and, overall, I did not really enjoy it. The key points regarding why follow. Hopefully, the opinion of a brain trained in science (generally, not psychology specifically) will shine through in this review rather than XY unconscious bias.

I found the lines between associative evidence and author opinion and between assumption and fact too often blurred when it came to the content compatible with the author’s opinion. The effect of this was an overstating of the strength of the compatible evidence and author opinion. This is especially disappointing as I find myself mostly agreeing with many of the author’s general opinions. While this blurring might not be picked up by the lay reader, it damages the actual strength of the evidence for the scientific reader. Taking one example from p.118: “our brain will act like an eager deep learning system and soak prejudices like the ones I just told you about” (“will” makes this a very definitive statement). One of those deep-learning machines we had been just told about is the Microsoft chatbot Tay. “Tay went from tweeting about how ‘humans are supercool’ to becoming a ‘sexist, racist asshole’ within sixteen hours” (p.358). So, I dare not think what the ~300,000 hours of information absorbing by my “deep-learning” brain “will” mean for me. Another example is on p.186, the “suggested that babies...actively engage” was shortly followed and translated into the more definitive “babies can rapidly acquire” (suggested ≠ can). Such blurring was too abundant throughout.



Babies' brains are exposed to gendered stimuli from birth

To balance with a positive, some of the insights provided into inferences made from psychology experiments (especially in babies) are fascinating to read, albeit the fascination is from disbelief. Did you know, following mini-morality plays, 3-month-old babies signal moral approval for the good character in the play by reaching for them when given the choice of good or bad character (p.190)? Getting beyond the fact that these are morality evaluations in 3-month-olds, and then the massive potential for experimenter bias, you might ask why the scientists conclude that this reflects babies' moral approval for the good character rather than them reaching for the person they might consider easier to exploit/manipulate for food or entertainment. The latter is my own suggestion of a potential inference. If you read this book, I expect you shall not be short of your own concerning such concepts.

Some difficult-to-believe inferences are even built on each other: A baby opening its mouth is an indication of interest in an object or the object being novel... Identification of novelty is a measure of environmental impact on baby brain development.... Others can somewhat contradict each other: Babies appear to be aware that a conversation will quickly break

down if there is no mutual gaze between speakers as determined by them being happier if the gaze from a face is on them, but in a different experiment they will happily focus on the object of someone's gaze ....!?!

Even though a massive research undertaking has undoubtedly been performed to produce this work, the central argument would probably be best served by describing a normal distribution with an x-axis title of "insert personality trait score here". Essentially, for all such traits and abilities, we are all on a spectrum. Myth = shattered. Perhaps even use two overlapping distributions, one for individuals with XY chromosome pairs and one for individuals with XX chromosome pairs, and one slightly left or right shifted or skewed or leptokurtic or platykurtic, depending on your trait and population and explain how the averages cannot and should not be considered as being able to correspond to individuals.

The conclusion section summarises the most interesting information from the preceding chapters quite well and includes potential explanatory variables for any differences in averages or shapes of distributions. The other 300+ pages of forced comparisons

and assumptions that come across as fact I probably could have done without.

Overall, my notes whilst reading could be used to write half a book (I got tired of noting the same issues about halfway through) about all of the content that I do not like. Yet, I am inclined to agree with the author's general opinions, albeit neither convinced by some of the inferences from psychological studies nor how the author formulates her arguments (I can at least envisage how it could be formulated with more balance). Simply, the content seems a better fit for her opinions. As for shattering the myth of the female brain, the author makes a good argument for how biased nurture could result in a "female brain" so I am not sure about that.

Most importantly, in the conclusion she states: *"We can ensure that brain owners are aware of just how flexible and malleable an asset they have in their heads, but also make our society aware of the brain-changing nature of negative stereotypes (of any kind)... which can lead to self-silencing, self-blame, self-criticism and plummeting self-esteem."* Irrespective of what theory/stance this arises from, it is a message that should not be understated.

## Vitamin D

One hundred years of the sunshine vitamin



*Dr Alexander T Carswell*

University of East Anglia, Norwich, UK



*Professor William D Fraser*

University of East Anglia, Norwich, UK

A century ago, the industrialised towns and cities of Northern Europe and North America were filled with dark streets overshadowed by buildings, and covered by skies polluted by the smog of industry (Fig.1). Winter daylight hours were short and sunshine weak. Residents were exposed to limited sunlight and endured a post-war diet with little milk, cheese, butter, cooking fats, or meat. Rickets — a painful and disabling childhood disease characterised by weak, soft bones — was endemic with an estimated prevalence of 75–98%. The long bones in the legs of children with rickets were so poorly mineralised they could not resist the forces of tension and compression applied by their body's weight. This caused lateral bending and a bow-legged or knock-knee appearance (see cover). Although rickets was first described in the 17th century, its cause remained unknown. Pioneering studies in the early 20th century showed that cod liver oil and sunlight could prevent and cure rickets. This led to the identification of an anti-rachitic factor crucial for bone mineralisation, named vitamin D, and commenced a century of fascinating research.

### A, B, C, D — the discovery of the fourth vitamin

Following the understanding that diseases like beriberi and scurvy were caused by dietary deficiencies in vitamins B and C, respectively, it was thought that rickets might similarly be caused by a nutrient deficiency. At the start of the 20th century, rickets was so wildly prevalent in the UK that it was known as “the English disease”. In response to this and its possible dietary cause, the biochemist Edward Mellanby demonstrated in 1919 that dogs caged indoors (thereby inadvertently deprived of the sun's ultraviolet radiation), and fed a diet of mainly oats, developed rickets. Mellanby found that cod liver oil was able to

cure the disease. Vitamin A was thought by Mellanby to be the nutritional factor in cod liver oil responsible for its curative properties. Testing this hypothesis in 1922, Elmer McCollum and colleagues in the US cleverly found that destroying vitamin A within cod liver oil did not impair its anti-rachitic ability. They concluded that the nutritional factor responsible for curing rickets was a distinct vitamin, the fourth to be identified, and thus named it vitamin D (DeLuca, 2016).

In Austria, Kurt Huldschinsky in 1919, and Harriette Chick and colleagues in 1923, discovered that rickets could also be cured by exposing rachitic children to summer sunlight or artificial ultraviolet light. Similarly, the US-based laboratories of Harry Steenbock





**Figure 1. Photograph of a dark residential alleyway in Glasgow, UK, taken in 1868.** These living conditions contributed to the prevalence of rickets in the 19th and early 20th centuries. Public domain image from the Los Angeles County Museum of Art [www.bitly.3lwFUr3](http://www.bitly.3lwFUr3)

and Alfred Hess independently demonstrated in 1924 that irradiating animals or their food with ultraviolet light could prevent or cure rickets. With these apparently shared curative properties of cod liver oil and sunlight, Steenbock demonstrated in 1925 that irradiation converted an inactive lipid into the anti-rachitic factor (i.e. vitamin D) (DeLuca, 2016). These monumental discoveries led to the use of sun lamps to irradiate children, as well as the introduction of staple foods enriched with vitamin D, ultimately eliminating rickets as a major medical problem.

### Vitamin D metabolism

In the 1930s, the structure of vitamin D<sub>2</sub> was first identified by Askew *et al.* in the UK. Adolf Windaus and colleagues in Germany then isolated and identified the structure of vitamin D<sub>3</sub> for the first time (DeLuca, 2016). Vitamin D<sub>2</sub> is the plant-derived form, and vitamin D<sub>3</sub> the endogenous form synthesised in the skin. Vitamin D<sub>2</sub> was identified by irradiating

plant sterols, and vitamin D<sub>3</sub> by irradiating 7-dehydrocholesterol, its lipid precursor within the skin. Ultraviolet B radiation is absorbed by 7-dehydrocholesterol to form pre-vitamin D<sub>3</sub>, which is converted to vitamin D<sub>3</sub>, before entering the bloodstream bound to vitamin D binding protein (Fig.2). Vitamin D is fat soluble. Dietary vitamin D<sub>2</sub> and D<sub>3</sub> are incorporated into chylomicrons (large lipoprotein particles) before entering the lymphatic system and then the circulation also bound to vitamin D binding protein.

In the liver, vitamin D undergoes a hydroxylation reaction to form 25-hydroxyvitamin D [25(OH)D], the major circulating metabolite, the concentration of which is used to determine vitamin D status (Table 1). In the kidneys, 25(OH)D is hydroxylated to 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D], the biologically active form of vitamin D (Fig.2). The structures of 25(OH)D and 1,25(OH)<sub>2</sub>D were identified in the US by Michael Holick, Hector DeLuca, and colleagues in the 1960s and 1970s.

To limit excessive 1,25(OH)<sub>2</sub>D synthesis and activity, the renal hydroxylation reaction producing 1,25(OH)<sub>2</sub>D is tightly regulated by parathyroid hormone, vitamin D itself, and phosphate. Parathyroid hormone stimulates hydroxylation, whereas 1,25(OH)<sub>2</sub>D and phosphate inhibit 1,25(OH)<sub>2</sub>D production. Although still categorised as a vitamin, the name “vitamin D” is a misnomer. Due to its endogenous synthesis in the skin, and owing to the fact that even the fraction gained from the diet (typically 10%) must be metabolised to its active form, vitamin D is actually a steroid hormone.

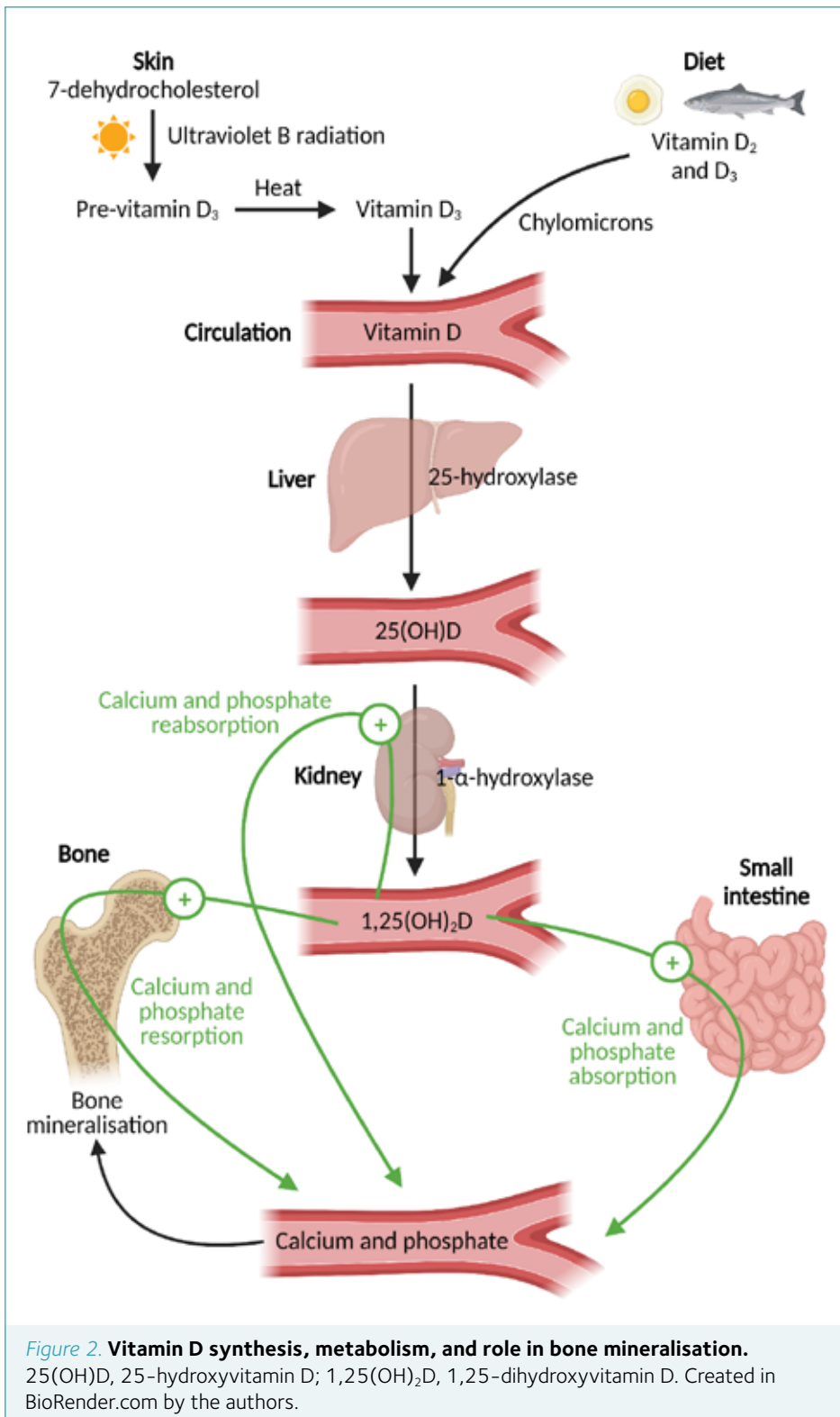
### Bone mineralisation

The primary and classical physiological function of vitamin D is to maintain calcium and phosphate concentrations within their normal physiological ranges. Accordingly, vitamin D is essential for the mineralisation of bone. Serum 1,25(OH)<sub>2</sub>D binds with nuclear vitamin D receptors (a transcription factor identified in 1973) to induce the expression of vitamin D target genes. The effects of this are three-fold: 1) augmentation of calcium absorption within the small intestine by increasing the expression of epithelial calcium channels and pumps; 2) promotion of renal calcium reabsorption in the distal tubule; 3) stimulation of osteoclastic bone resorption to release calcium into the circulation. Vitamin D also promotes phosphate absorption in the small intestine, reabsorption in the kidney, and resorption in bone. The 1952 discovery that vitamin D causes the mobilisation of calcium from bone into the circulation (i.e. decalcification) may appear counterproductive for bone strength. However, the indirect effects of vitamin D on bone (in the small intestine and kidney) supersede the direct effects. This results in a net increase in the flux of calcium into bone and augmented mineralisation of osteoid (Fig.2).

### Beyond bone

The identification of vitamin D receptors in numerous body tissues indicates vitamin D has functions beyond maintaining calcium and phosphate homeostasis (Rosen *et al.*, 2012). Evidence of extraskeletal effects of vitamin D has accumulated in the 21st century, including direct effects on aspects of innate and acquired immunity, skeletal and smooth muscle, and the cardiovascular system. Some effects of 1,25(OH)<sub>2</sub>D are more immediate than those requiring gene transcription and translation and are understood to be mediated by membrane-bound vitamin D receptors and non-genomic pathways.

Vitamin D has been shown to enhance the innate immune response by inducing



and inhibiting cell proliferation; however, the strength of the existing evidence is insufficient for a definitive conclusion to be reached (Scientific Advisory Committee on Nutrition, 2016). The development, repair, and remodelling of skeletal muscle may be influenced by vitamin D, giving it the ability to affect muscle function. Vitamin D has been demonstrated to affect muscle metabolism and intracellular calcium handling, and to improve mitochondrial oxidative function (Girgis *et al.*, 2014). Vitamin D has also been shown to mitigate endothelial dysfunction (potentially by stimulating the release of the vasodilator nitric oxide) and may, therefore, be beneficial for cardiovascular health (Wolf *et al.*, 2020).

### The next one hundred years...?

#### Cause and effect

Controversy about the extent of vitamin D's influence beyond bone mineralisation exists. With most evidence derived from correlative observational studies, there is a paucity of research demonstrating cause and effect. Positive associations between vitamin D status and physical performance or cardiovascular health may be due to reverse causation; whereby more active, healthier individuals may spend more time outdoors exposed to sunlight, and thereby have superior vitamin D status than more sedentary individuals. Two recent, large, randomised, double-blind, placebo-controlled trials found that vitamin D supplementation did not reduce the incidence of cancer, cardiovascular events (Manson *et al.*, 2019), or type 2 diabetes (Pittas *et al.*, 2019). Further empirical data are needed to clearly elucidate the role of vitamin D metabolites on extraskeletal outcomes, whilst controlling for baseline 25(OH)D concentrations. For beneficial or ergogenic effects of vitamin D to be detected, vitamin D-deficient individuals ought to be targeted (Table 1). However, this approach will raise ethical concerns for individuals allocated to control arms.

#### Endemic deficiency

Even in the 21st century, vitamin D deficiency and rickets continue to be a problem in some regions (e.g. North Africa and the Middle East) and ethnic groups (e.g. South Asians and Africans living in high-income countries), particularly where exposure to sunlight is compromised, for instance by residing indoors during daylight hours or wearing clothing that covers the skin. Individuals with darker skin (containing more melanin) who have emigrated to temperate latitudes are at increased risk of deficiency due to melanin's absorption of ultraviolet radiation. Recommended safe sunlight exposure guidelines for vitamin D sufficiency (15 min daily UK summer sunlight exposure to one third of the skin surface area [Advisory Group on Non-ionising Radiation, 2017]) need to be updated to include advice for non-white skinned individuals.

antimicrobial proteins, which, in forming a first line of defence against invading pathogens, may help prevent upper respiratory tract infections (Martineau *et al.*, 2017). Vitamin D may also have an anti-inflammatory or tolerogenic effect, whereby the severity or duration of infection symptoms are reduced. Despite the noise from some underpowered trials and unreliable observational studies at the height of the pandemic, evidence is sparse for a consensus to be reached on whether vitamin D can reduce the severity of COVID-19. Vitamin D may have a role in protecting against cancer and reducing cancer development by enhancing cell apoptosis

Circulating 25(OH)D concentration (nmol/L)	Vitamin D status
<30	Deficient
30–50	Insufficient
≥50	Sufficient

**Table 1: Vitamin D status.** Thresholds defined by the US Institute of Medicine (Scientific Advisory Committee on Nutrition, 2016).

### Recommended intake

Debate continues around the thresholds for vitamin D deficiency, insufficiency, sufficiency, and a proposed optimum vitamin D status. Defined for skeletal health (Table 1), evidence is lacking to support specific recommendations for cardiovascular health, physical performance, or protection against respiratory infections. Consequently, recommended daily intakes of vitamin D continue to be debated. In the UK, a vitamin D reference nutrient intake/safe intake of 400 IU/day is recommended for everyone aged ≥1 year to maintain serum 25(OH)D ≥25 nmol/L (Scientific Advisory Committee on Nutrition, 2016). At UK latitudes (50–60°N), the strength of solar ultraviolet B radiation is inadequate to make enough vitamin D between October and March, therefore the UK government recommends everyone should consider taking a daily supplement containing 400 IU vitamin D<sub>3</sub> during these months. An upper intake limit of 4000 IU/day is advised to avoid vitamin D intoxication and hypercalcaemia. Even without evidence of toxicity, high-dose vitamin D supplementation may be detrimental (Owens *et al.*, 2017).

### Metabolites

Serum 25(OH)D has recently been purported to be a poor biomarker of vitamin D status, despite its use for decades. Serum 25(OH)D concentration does not differentiate between 25(OH)D bound to vitamin D binding protein or albumin (approximately 99%), and unbound (and thus bioavailable) 25(OH)D. Bioavailable metabolites may more strongly correlate with clinical outcomes. The ratio of 24,25-dihydroxyvitamin D [24,25(OH)<sub>2</sub>D, a product of 25(OH)D] to 25(OH)D is independent of vitamin D binding protein concentrations and might be a better marker of vitamin D status (Ginsberg *et al.*, 2021).

Most vitamin D metabolites (33 have been identified) are deemed to be inactive or intermediary waste products. However, thanks to recent advances in technology enabling the separation and quantification of metabolites, interest in possible biological actions and variation in their relative concentrations has

risen (Tang *et al.*, 2019). Potential functions of 24,25(OH)<sub>2</sub>D in fracture repair, and the existence of a 24,25(OH)<sub>2</sub>D-specific receptor have emerged. Whether supplementation with metabolites downstream of 25(OH)D can positively influence clinical or other meaningful outcomes warrants investigation.

### Genetics

Polymorphisms in the genes that encode for the vitamin D receptor, binding protein, or hydroxylation enzymes may be responsible for some inter-individual variability in the vitamin D endocrine system (Girgis *et al.*, 2014). The impact of an individual's genotype on vitamin D status, and physiological function remains to be fully determined.

### Ageing

Lower availability of 7-dehydrocholesterol in ageing skin and reduced sun exposure in the frail are risk factors for vitamin D deficiency. Vitamin D-deficient adults can develop osteomalacia, which is characterised by weak, inadequately mineralised bones at increased risk of fracture. Vitamin D deficiency during adulthood can also contribute to and exacerbate osteopenia (loss of bone mass) and osteoporosis, heightening fracture risk. With life expectancies increasing globally, and the ageing demographics of developed countries, maintaining vitamin D sufficiency from cradle to grave is of increasing importance, at least to maximise the accumulation and maintenance of bone mineral density. Biofortification of a wider array of foods with vitamin D may be a convenient and cost-effective means of providing an adequate vitamin D intake throughout the lifecycle. Vitamin D is stored in body fat. With the prevalence of overweight and obese individuals increasing, releasing vitamin D from adipose tissue could prove to be an effective way to avoid vitamin D deficiency.

### Climate change

More frequent extremes of low and high temperatures due to global warming may result in reduced skin exposure to sunlight (with individuals covering their skin with clothing or sunscreen, and spending more time indoors). Rising temperatures may also accelerate migration away from the equator to more temperate latitudes. Climate change could therefore reduce endogenous vitamin D synthesis and increase the risk of vitamin D deficiency. Appropriate supplementation and safe sun exposure guidance to mitigate these knock-on effects of climate change may be necessary.

### Final thought

If the 1920s were the dawn for the study of vitamin D, the sun is far from setting on this remarkable molecule.

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## Phototransduction

### The decline and fall of the calcium theory



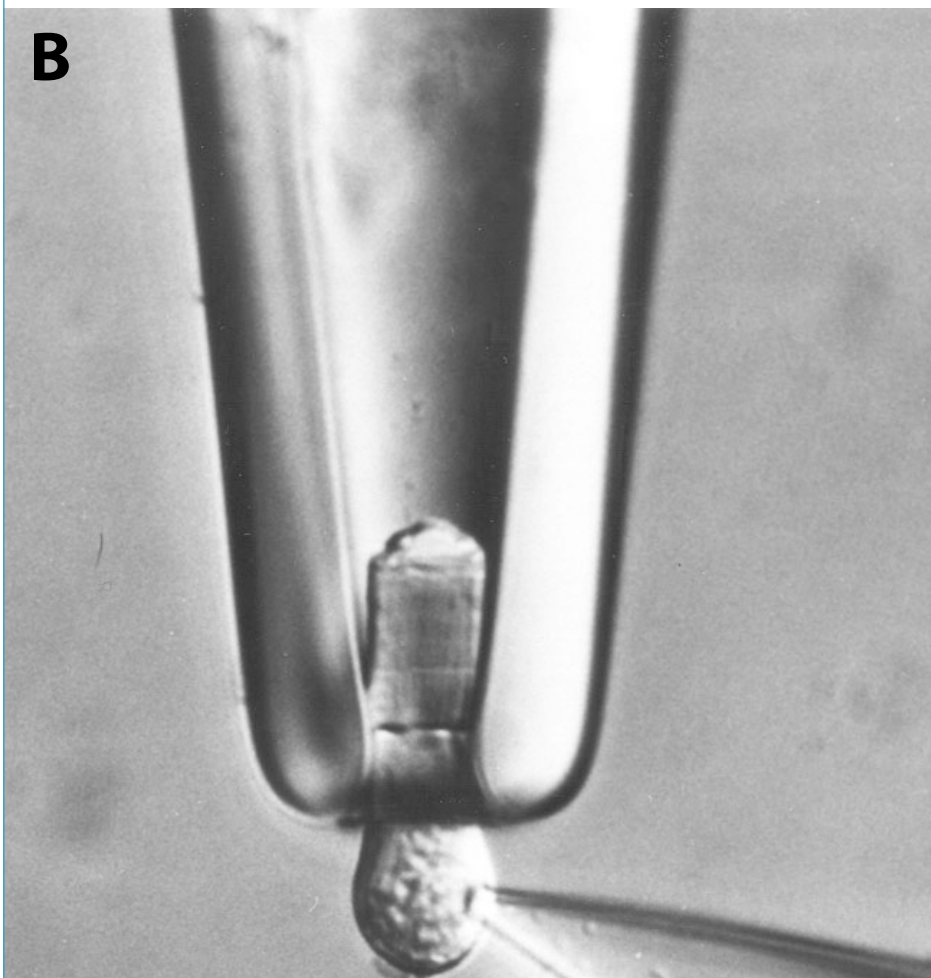
*Jonathan A. Coles*

Honorary Research Fellow,  
University of Glasgow

The death of the calcium theory of phototransduction was announced after lunch at the Züricher Hotel in Berlin on Friday 30 November 1984 to an international audience of some 40 researchers working on vision. The announcement instantly resolved a fierce debate that had been going on for almost 20 years and we were given the afternoon off to try to recover from the shock.

In 1965 when the pathway of sensory transduction from stimulus to electrical signal was unknown for any of the senses, vision had the attraction of the precision of the stimulus: a photon absorbed by a rhodopsin molecule. It was known that most signalling in the nervous system resulted from an increase in membrane permeability, particularly to sodium, whose influx depolarised the cell. Some invertebrate photoreceptors, such as the giant cells of the ventral eye of the horseshoe crab, *Limulus*, had been studied and they depolarised in response to light, as expected. In vertebrate retina, Svaetichin (1953) recorded from sites with a negative resting potential that gave a hyperpolarising, rather than a depolarising, response to light. Svaetichin's claim that these recordings were from photoreceptors was met with justifiable scepticism – for one thing, these recordings were too easy to make. But it took several groups, working for over a decade, to understand the situation (see Tomita, 1965 for refs). Oikawa *et al.* (1959), working on carp retinas, showed that in most recordings, the response amplitude increased when the area stimulated by light increased, but in some it did not. They suggested that the first class were horizontal cells (which extend over an area including many photoreceptors) and the second class were the photoreceptors themselves, in this case, cones. Bortoff (1964) recorded from cells in the salamander, *Necturus*, which he identified

by dye labelling as rod photoreceptors and again these gave hyperpolarising responses to light. Meanwhile, Tsuneo Tomita and his students in Tokyo were working carefully and methodically to decipher the system. They introduced a range of new techniques, most notably a jolter that used an electromagnetic diaphragm to jolt the retina onto the microelectrode (Tomita *et al.*, 1967; Kaneko, 2021). They also built an elaborate light stimulator that could measure the spectral response of a cell quickly, before the electrode fell out, and used it to show that responses from cones in carp supported Young's trichromatic theory of colour vision. Toyoda *et al.* (1969) showed that the light-induced hyperpolarisation in rods was due to a fall in membrane conductance. This result defined a major problem: in rods, the rhodopsin that is isomerised by photons and initiates the receptor potential is in the membranes of the discs or sacs that are stacked inside the outer segment, and not attached to the surface membrane (Fig. 1A). A tempting idea was that the photoisomerisation of rhodopsin caused some ion or molecule to diffuse through the cytoplasm from the disc and close channels on the surface membrane. Protons were quickly ruled out, but the hypothesis of Yoshikami and Hagins (1971) that the internal transmitter was calcium, received experimental support for a decade or so. On a different tack, cyclic adenosine monophosphate was known to



be a common internal messenger and the enzymes required for its production (cyclase) and hydrolysis (phosphodiesterase) were looked for, and found, in photoreceptors. But in rod outer segments, it was the guanosine system, rather than the adenosine, that was far more active, both a guanylate cyclase (Goridis *et al.*, 1973) and a guanylate phosphodiesterase. Photoisomerisation of a single rhodopsin molecule rapidly activated up to 500 molecules of phosphodiesterase converting cGMP to 5'GMP (Yee and Liebman, 1978). Manipulating cGMP levels changed the membrane potential. But how would a change in the concentration of cGMP change the membrane resistance? Its expected action was to phosphorylate proteins, or perhaps a light-activated GTPase was involved (Fleischman and Denisevich, 1979).

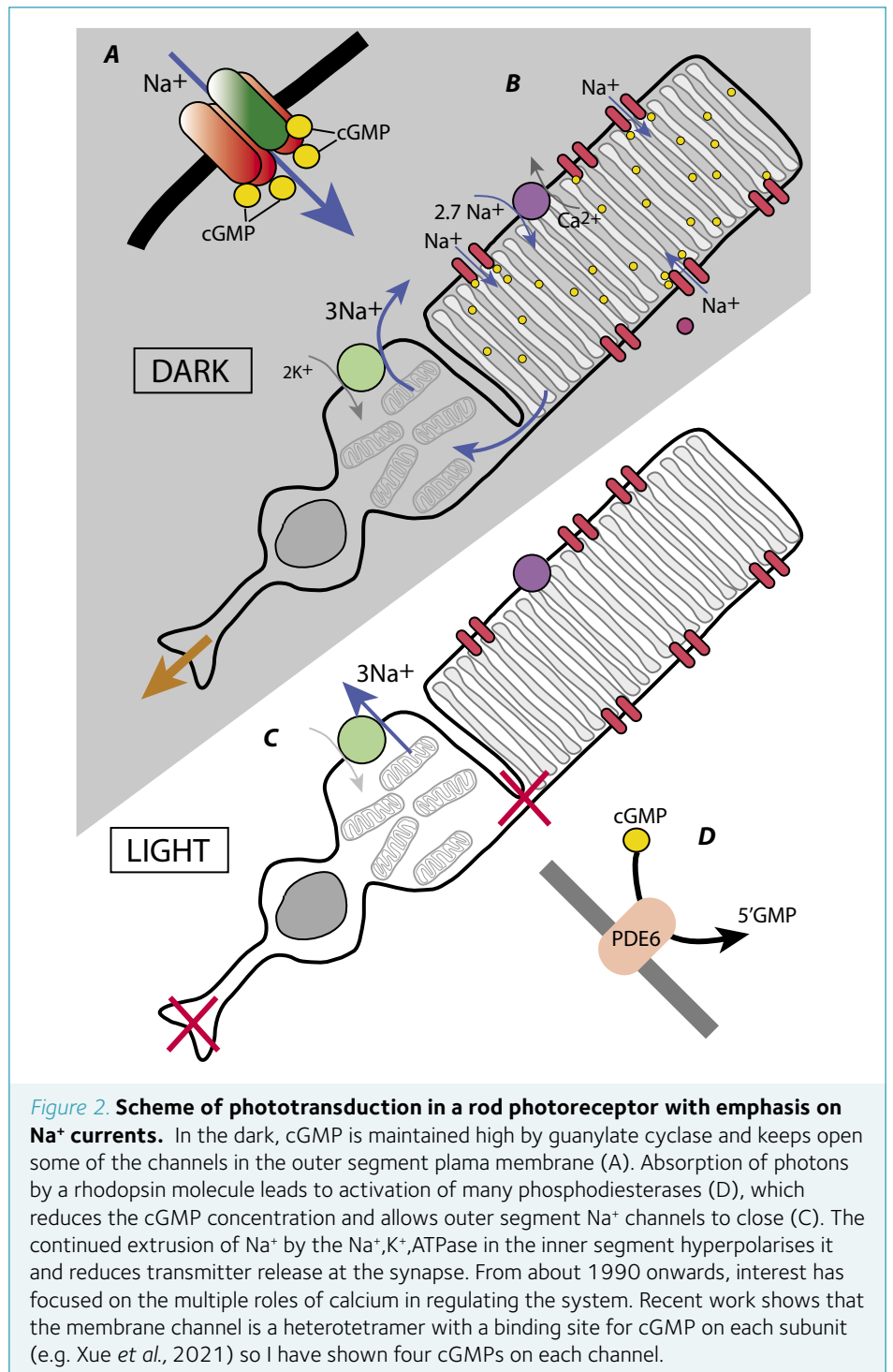
In the 1970s several new techniques were brought to bear. Yau and colleagues independently developed a way of measuring the current flowing through the rod outer segment membrane by sucking the outer segment into the tip of a pipette (Yau *et al.*, 1977) and, with dexterity, this could be combined with the patch electrode technique definitively described by Hamill *et al.* (1981) (see Fig.1B). In 1980, Gold and Korenbrot devised a calcium-sensitive membrane electrode on which they placed a retina and showed that light stimulation caused calcium release from rod outer segments.

It should be remembered that news was transmitted by post, by visits and sometimes by telephone, and that checking the latest literature meant going to the library and thumbing through journals. Working out a coherent description of transduction in a vertebrate sensory cell was an obvious prize and papers came tumbling out, often beautifully done and with considered but inconclusive discussions; there were, for example, six papers in 1984 on the subject in *Nature* alone.

This was the background to the Dahlem "Konferenz" (more a "workshop") that was held in 1984 on "The Molecular Mechanisms of Photoreception". Dahlem, a suburb of Berlin, is where Otto Warburg had done his biochemistry research and, in 1933, it had a fleeting connection with phototransduction when George Wald visited and found vitamin A (retinal) in the retina. Since 1974, several Dahlem Workshops a year have been held in what was the enclave of West Berlin. They are limited to 40 participants, discussion documents are prepared beforehand and, for much of the time, the meeting is split into four working groups that produce reports on different aspects. For the 1984 phototransduction meeting, the scientific organiser was Hennig Stieve, who worked on *Limulus* ventral photoreceptor, and the detailed management was by Silke Bernhard, who had 10 years of experience. The dates were 25–30 November 1984, which turned

**Figure 1. A.** Electron micrograph of a frog rod outer segment showing the evenly stacked 'discs' not contacting the surface membrane (arrow). The width of the figure is about 3.0  $\mu\text{m}$ . © Nilsson SE (1965) *Journal of Ultrastructure Research*, **12** 207–231. [http://doi.org/10.1016/s0022-5320\(65\)80016-8](http://doi.org/10.1016/s0022-5320(65)80016-8). **B.** A rod isolated from a larval tiger salamander and held by a suction electrode, which measures current. A patch pipette was then mounted on a micromanipulator and manoeuvred in the dark until "with a little luck, the new patch pipette appeared on the screen of the TV monitor". The cell membrane was ruptured by the pipette, which was then used to introduce a calcium chelator into the cell; this increased the dark current. The diameter of the outer segment is about 10  $\mu\text{m}$ . © Lamb *et al.* (1986) *Journal of Physiology*, **372**(1), 315–349. <http://doi.org/10.1113/jphysiol.1986.sp016011>

It should be remembered that news was transmitted by post, by visits and sometimes by telephone, and that checking the latest literature meant going to the library and thumbing through journals.



out to be important. Among other things, a key paper on "Electrogenic Na-Ca exchange in retinal rod outer segment" by Yau and Nakatani (1984) had been published on 18 October.

I was something of an outsider and was shamefully relaxed about it. I enjoyed the luxury hotel overlooking the Tiergarten park, and the delightful small restaurants that Silke, a perfect host, took us to in the evenings. Of course, all this was in the Western sector. Despite the Berlin Wall, the underground railway could be used to cross the border, the main incentive being to visit the Pergamon museum with its outstanding collection of archeological treasures.

A rule at the Dahlem Workshops was that no slides were to be shown. However, early on in the meeting, Trevor Lamb, a tall, bearded New Zealander, twisted Silke's arm and was allowed to show one slide, which showed that when intracellular calcium was chelated the photoresponse increased rather than decreased (Matthews *et al.*, 1985). The meeting went on, with a curious air of uneasiness as nearly all the participants wondered what the role of cGMP was. Then, after lunch on the last day, it was revealed that two reviewers and a *Nature* Editor (all present at the meeting) had a manuscript received from the USSR Academy of Sciences at Pushchino, near Moscow, on 16 November, nine days before the meeting. Defying general wisdom, Fesenko, Kolesnikov

and Lyubarsky (Fesenko *et al.*, 1985) had applied cGMP directly to the cytoplasmic face of the surface membrane of a rod outer segment and found that it increased the conductance. This result filled the missing link in vertebrate phototransduction: photoisomerisation of rhodopsin led to activation of the phosphodiesterase, which reduced cGMP levels and decreased the membrane conductance (Fig.2). As the meeting report in *Nature* (Altman, 1985) put it, the announcement “electrified the whole meeting”. Disclosing results from a paper under review was not quite proper, and *Nature* had politely waited until publication of the Fesenko paper, on 24 January 1985, before publishing its report. Curiously, both this report, and the introduction to the proceedings book (Stieve, 1986) make the same mistake in the references, putting the publication of the Fesenko paper in 1984 rather than 1985, a subconscious attempt to smooth out history, perhaps. The *Nature* report also announced three further papers in press, all supporting the cGMP theory and these were published together on 14 February (Yau and Nakatani, 1985; Matthews *et al.*, 1985; Cobbs and Pugh, 1985). The “received on” dates show that all three were under review at the time of the meeting, at which four of the authors were present (and, presumably, some of the reviewers). The atmosphere in the “Internal Messengers” working group must have been interesting.

What has happened since the meeting? Most of the participants continued long and productive careers in vision: a detailed understanding of the regulation of transduction by calcium, the molecular structures of the proteins and how those structures transform, the evolution of photoreceptors, the causes of eye disease. Of the three authors of the crucial paper, Kolesnikov and Lyubarsky continued on vision, Lyubarsky having moved to Philadelphia, while Kolesnikov stayed in Pushchino. Fesenko, also in Pushchino, continues to publish frenetically on subjects that usually include magnetic fields, electromagnetic radiation or cryoprotection.

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## Stem cell-based therapies for musculoskeletal regeneration

Role of the microenvironment in augmenting regenerative medicine therapies by elucidating stem cell physiology



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All the information required to define a multicellular organism resides in a single cell, the zygote or the single-cell embryo. And therein lies the origins of the concept of a “stem cell” as a highly specialised cell containing all the information required to generate a complex multicellular organism. Stem cells are a key component of the multidisciplinary tissue engineering paradigm used for the generation of living tissues and organs *ex vivo* (outside the body). The bioengineered tissues and organs are implanted *in vivo* to improve or restore normal biological function in regenerative medicine therapies for disorders of complex organ systems such as the musculoskeletal system. A wide array of regenerative medicine strategies, ranging from stem cell-based therapies to the application of tissue-engineered products, have been applied for the treatment of bone defects, articular cartilage lesions, disorders of the spine and tendon/ligament injuries. Further advances in the development of improved musculoskeletal regenerative medicine therapies will be guided by a detailed understanding of underlying mechanisms governing the homeostasis between stem cell renewal and differentiation.

Stem cells reside in a specialised microenvironment, the stem cell niche, and differentiate in diverse tissue microenvironments after circulating away from their niches. Dissecting the key roles of the stem cell niche and the diverse tissue microenvironments in regulating stem cell self-renewal and lineage commitment will contribute to greater understanding of the underlying mechanisms governing stem cell function. Additionally, comprehensive insight into the interactions between stem cells and other components of the stem cell niche, and the effect of extracellular matrix (ECM) elasticity/stiffness on stem cell lineage specification in diverse tissue microenvironments will inform strategies

for improved stem cell culture and differentiation into desired musculoskeletal lineages.

### Types and characteristics of stem cells used in musculoskeletal regeneration

Stem cells are defined as highly specialised cells characterised by the capacity for prolonged self-renewal under controlled conditions and, while maintaining their undifferentiated state, are able to differentiate into a variety of mature cell types based on their varying differentiation potential or potency. Based on their



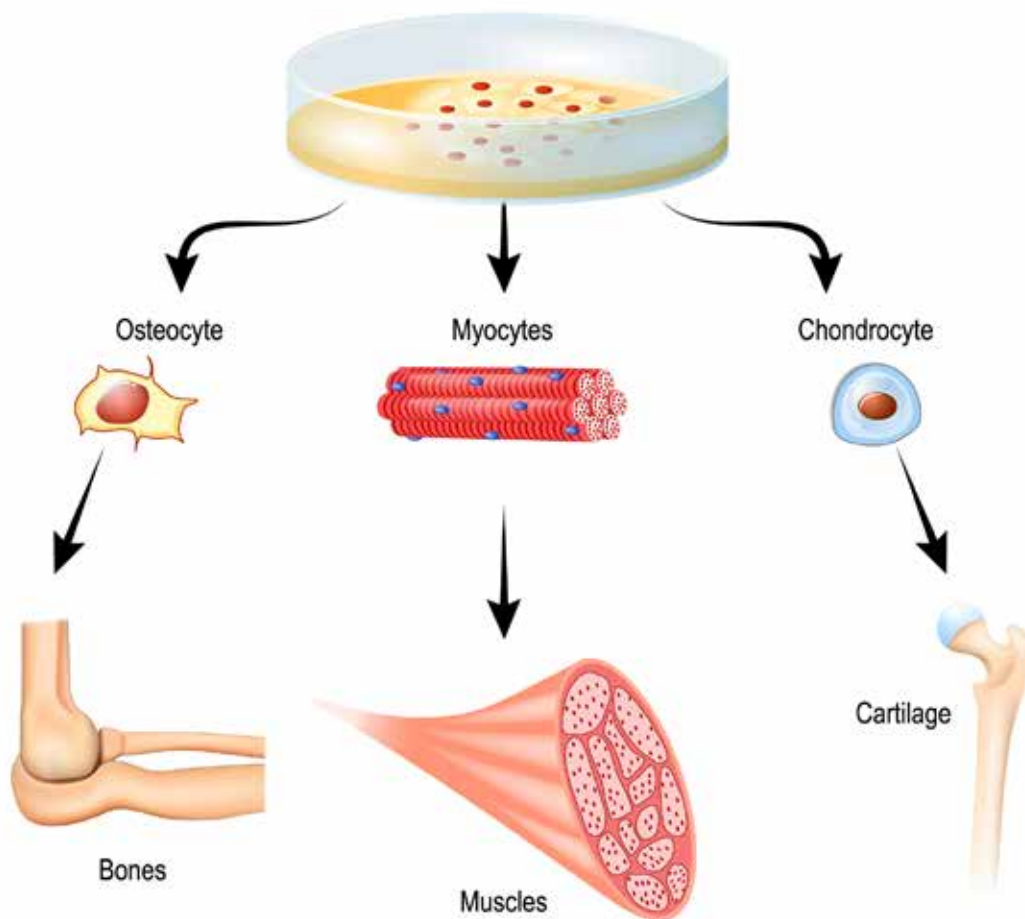


Figure 1. Mesenchymal stem cell differentiation ©Shutterstock.

differentiation ability, stem cells are categorised as:

- totipotent – able to differentiate into all cell types and extra-embryonic tissues (e.g. the zygote)
- pluripotent – able to differentiate into all cell types of the three germ layers e.g. embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs)
- multipotent – able to differentiate into the multiple cell types constituting the tissue of origin (e.g. haematopoietic stem cells, mesenchymal stem cells (MSCs))
- unipotent – able to differentiate into a single cell type (e.g. spermatogonia giving rise only to the sperm)

ESCs constitute an inexhaustible source of self-renewing cells capable of differentiating into the principal musculoskeletal lineages, namely bone, cartilage, muscle and fat, making them a viable option for application in musculoskeletal regeneration. Allogeneic human ESCs (hESCs) have been successfully differentiated into chondrocytes, which in turn have been used to tissue engineer

mechanically competent 3D hyaline cartilage constructs that have the potential to repair focal defects in articular cartilage, widely regarded to be an immune-privileged skeletal tissue (Griffith *et al.*, 2021). However, ethical concerns related to the embryonic origin of hESCs, predisposition of hESCs to form teratomas and the risk of immune rejection due to debatable immune-privileged properties have limited the application of hESCs in musculoskeletal regeneration. While potential issues with immunogenicity could be ameliorated by generating banks of clinical-grade hESC lines, which are human leukocyte antigen-matched to groups of individuals, it is important that the additional challenge of aneuploidy (presence of an abnormal number of chromosomes) arising from the prolonged culture of hESCs is addressed before the application of hESCs in the clinic.

Human iPSCs (hiPSCs) circumvent the ethical issues associated with the use of hESCs and constitute an autologous pluripotent stem cell population suited for use in personalised regenerative medicine approaches. However, there are challenges related to their use. These include biased differentiation potential of hiPSCs into their

lineage of origin due to the retention of residual epigenetic memory from the donor cell source, potential tumorigenicity, genetic instability and phenotypic heterogeneity. Derivation of clinical-grade hiPSCs using transient, integration-free methods for the delivery of reprogramming factors without causing insertional inactivation of tumour suppressor genes and/or activation of oncogenes also remains challenging.

The term “mesenchymal stem cell” was originally coined to describe a hypothetical common progenitor of a wide range of non-haematopoietic, non-epithelial, mesodermal tissues. MSCs used in musculoskeletal regeneration have been isolated from umbilical cord blood and an array of adult tissues. These include postnatal human bone marrow stromal tissue (referred to as skeletal stem cells (SSCs)), adipose tissue, skeletal muscles (referred to as satellite cells), cartilage, synovium, ligaments and tendons. Multipotent MSCs are acknowledged as promising autologous cell populations for musculoskeletal regeneration due to their relative ease of isolation and expansion *in vitro*, perceived immunomodulatory properties, limited tumorigenicity and robust ability to

differentiate into the major cell types of the musculoskeletal system due to their mesodermal origin.

The application of MSCs for musculoskeletal regeneration requires expansion of the MSC populations under defined conditions to generate an optimal number of cells without altering their phenotype or genotype. However, bone marrow-derived MSCs (BMSCs), the most widely used MSC population in musculoskeletal regeneration, exhibit limited cell proliferation ability and “replicative senescence” following successive subculture (Stenderup *et al.*, 2003). Furthermore, the ability of BMSCs to proliferate and differentiate declines with advancing age and they demonstrate considerable heterogeneity in their growth rate and differentiation potential (Phinney *et al.*, 1999; Stenderup *et al.*, 2003). Although there are no reports of spontaneous transformation of culture-expanded BMSCs and culture-induced genetic alterations in the BMSCs that could lead to tumour formation *in vivo*, it has been suggested that systemically administered BMSCs could be recruited to the tumour stroma and promote the growth of a latent tumour, as evidenced in some experimental cancer models (Lepperdinger *et al.*, 2008).

The overall safety record of BMSCs remains excellent; their ready accessibility from bone marrow and ability to differentiate into the principal skeletal cell lineages *in vivo* have driven the clinical application of this autologous MSC population in patient-tailored therapies for musculoskeletal regeneration.

## MSC-based therapies for musculoskeletal regeneration

The surgical technique of microfracture used to treat defects in articular cartilage relies on the creation of tiny fractures in the bone underlying the articular cartilage to stimulate the influx of SSCs and growth factors from the bone marrow to promote defect repair. MSC-enriched bone marrow, or concentrates thereof, or *in vitro* cultured MSCs have been directly injected into diseased tissue, such as the osteoarthritic knee joint, where the cells eventually populate the target site and stimulate repair via autocrine or paracrine pathways (Davatchi *et al.*, 2011; Emadedin *et al.*, 2012; Wong *et al.*, 2013). Similarly, injections of adipose tissue-derived MSCs (ADMSCs) are used to treat tendonitis as they are capable of differentiating into tendons.

When large defects in bone (caused by trauma, tumours, infection, aseptic loosening, or non-unions) and cartilage (caused by daily wear and tear, trauma due to sports injuries etc.) need to be repaired, stem cell delivery to the defect site is augmented by using biomaterials. Examples include the delivery of autologous MSCs using osteoconductive hydroxyapatite and calcium phosphate scaffolds to successfully treat large segmental bone defects (Quarto *et al.*, 2001). Osteocele® Plus, an advanced allograft cellular bone matrix containing MSCs and osteoprogenitor cells combined with demineralised bone matrix and cancellous bone, and the Trinity Evolution™ allograft, comprising cancellous bone with viable osteogenic and osteoprogenitor cells retained within the

matrix and a demineralised cortical bone component, have been used as substitutes for conventional autografts/allografts in spinal fusion and foot/ankle fusion surgeries (Rush, 2010; Ammerman *et al.*, 2013).

A mechanically stable living bone composite comprising of SSCs and milled allograft was impacted into necrotic bone in the femoral head and was shown to be an effective new treatment for focal early-stage avascular necrosis of the femoral head (Aarvold *et al.*, Surgeon, 2013). Cartistem®, a medicinal product comprising of culture-expanded allogeneic human umbilical cord blood-derived MSCs delivered using the hyaluronic acid hydrogel, was applied for the regeneration of painful full-thickness cartilage defects in patients with osteoarthritis of the knee joint (Park *et al.*, 2017).

Biomaterial-assisted cell delivery is further enhanced by the application of chemical cues, provided by growth factors and supplements, and mechanical stimuli, via dynamic culture in bioreactors, which facilitate the generation of 3D tissue-engineered constructs *ex vivo*. Upon implantation *in vivo*, tissue-engineered constructs have the potential to fill the entirety of the defects, integrate effectively with the surrounding host tissue, being structurally and mechanically analogous to the host tissue, and promote robust repair. Advances in tissue engineering have included the application of 3D computed tomography (CT) scanning and computer-aided design to bioengineer a bone graft, which was perfectly shaped in the form of the patient’s lower jaw bone/mandible, by fabricating a titanium mesh cage that was filled with hydroxyapatite,



Figure 2. Three-dimensional CT scan (left) after transplantation of the bone graft with enhancement of soft tissue (red) and repeat skeletal scintigraphy (right) with tracer enhancement showing continued bone remodelling and mineralisation (arrows). © Warnke PH *et al.* (2004) *Lancet* **364**, 766–770. [https://doi.org/10.1016/S0140-6736\(04\)16935-3](https://doi.org/10.1016/S0140-6736(04)16935-3).

infiltrated with recombinant human bone morphogenetic protein (osteogenic growth factor) and the patient's bone marrow containing SSCs (Fig.2). Following implantation of the vascularised bone graft into the lower jaw, the patient had an improved degree of mastication and was satisfied with the aesthetic outcome of the procedure (Warnke *et al.*, 2004). Similarly, bespoke titanium joint implants, fabricated using computer-aided design-computer-assisted manufacturing, were enhanced with autologous SSCs and used to treat patients with significant bone loss due to failed joint replacements, resulting in significant clinical and radiological improvements (Goriainov *et al.*, 2018).

Although significant advances have been made in stem cell-based musculoskeletal regenerative therapies, especially for bone and cartilage disorders, further developments in this field will be guided by comprehensive understanding of stem cell physiology and, critically, how the microenvironment modulates stem cell function in response to physiological challenges.

### Role of the microenvironment in stem cell self-renewal and lineage specification

Stem cells reside in the stem cell niche, a specialised microenvironment constituting the basic unit of tissue physiology. The niche prevents depletion of the stem cell pool, protects the host from excessive stem cell proliferation and integrates the signals that orchestrate stem cell lineage specification and participation in tissue generation, maintenance and repair. The niche is composed of supporting cells located in unique topological relationships with the stem cells, signalling factors and the ECM. Biochemical signals from the supporting cells in the stem cell niche have been identified as important paracrine regulators of stem cell function. Moreover, the ECM is a multifaceted component of the niche as, in addition to its structural role, it regulates stem cell function by integrating the mechanical and biochemical signals through mechanotransduction – the process of translating mechanical forces through signalling cascades to affect changes in cells.

The niche also functions as a physical anchor for stem cells, with adhesion molecules such as integrins anchoring the stem cells to the ECM. The stem cell retains its ability to self-renew by maintaining close contact with the niche. Occasionally, the stem cell divides parallel to the niche surface, ensuring that both daughter cells maintain contact with the niche and retain the ability to self-renew, thereby generating two stem cells. In contrast, by dividing perpendicular to the niche surface, the stem cell ensures that only one of the two daughter cells maintains contact with the

niche and retains the ability to self-renew, while the other daughter cell leaves the stem cell niche to differentiate into a functionally mature cell. Thus, niche-controlled stem cell divisions offer a greater degree of flexibility and are more commonly observed in adult MSCs (Knoblich, 2008).

As adult stem cells circulate away from their niches and engraft and differentiate within a range of tissues, they are confronted with a range of ECM microenvironments as physically distinct as muscle, bone etc. MSCs exhibit extreme sensitivity to the elasticity/stiffness of the ECM; matrix stiffness in turn directs MSC differentiation and commitment to a specific lineage or phenotype. A stiffer substrate mimicking the muscle matrix has been shown to drive MSC differentiation into the myogenic lineage, while a rigid matrix mimicking collagenous bone directs differentiation into an osteogenic lineage. Cytoskeletal non-muscle myosin isoforms (A, B, C) are involved in sensing matrix elasticity and tensioning the cortical actin structures, which in turn are linked to the focal-adhesion complexes that activate signalling molecules, the mechanotransducers, within the stem cells to affect phenotypic change (Engler *et al.*, 2006).

Thus, comprehensive understanding of the complex interplay between stem cells and their niches that regulates stem cell function, and the effect of the ECM associated with the diverse musculoskeletal microenvironments on stem cell lineage commitment, will inform the design of successful stem cell-based regenerative medicine strategies for musculoskeletal repair.

### Future directions

A thorough understanding of the constituents of the stem cell niche and dissection of the complex interactions between stem cells and other components of the niche provide a unique opportunity to reconstitute the stem cell niche *in vitro*, facilitating the successful expansion of stem cells and generation of reservoirs of stem cells for use in musculoskeletal regeneration therapies. Furthermore, greater insight into matrix elasticity-directed MSC lineage specification opens up avenues to design and fabricate customised biomaterials with optimum elastic properties that promote MSC differentiation into desired lineages to foster robust musculoskeletal regeneration.

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## The (concise) guides to pharmacology and what they provide for physiologists



### *Dr Steve Alexander*

University of Nottingham Medical School, UK

A colleague suggested that the major difference between physiologists and pharmacologists is that the former mostly use drugs with names, while the latter mostly use drugs with numbers. The point (I think) they were making was that there is a greater chance that physiologists work with more defined systems and signalling pathways than pharmacologists. I don't believe that to be true now, if ever it was. I would contend that a difference between the disciplines of physiology and pharmacology, while there are enormous overlaps, is that there is a wider use of concentration– and dose–response curves in pharmacology journals compared to physiology journals. (As is true of any generalisation, of course, there are always multiple examples of opposing evidence.)

### The Guide to Pharmacology database and NC-IUPHAR

What the [GuidetoPharmacology.org](http://GuidetoPharmacology.org) online database and the associated Concise Guides to Pharmacology aim to do is to make life easier for ANY scientist making use of drugs. The Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR), which was established in 1987 and which I've chaired since 2015, has more than 100 subcommittees responsible for providing consensus information on families of pharmacological targets: receptors, transporters, enzymes and ion channels. Since the inception of NC-IUPHAR, close to 1,000 altruistic scientists worldwide have contributed time and information to the database, via a team of curators based at the University of Edinburgh, UK. The information the subcommittees collate includes rational, systematic nomenclature on their family of drug targets, based on

a system initially defined for receptors (Vanhoutte *et al.*, 1996). This ensures that biological scientists are all using the same language and avoids confusion. They also provide data on the characteristics of the distinct molecular targets, which might be biochemical, biophysical or pharmacological. For ion channels, for example, associated or ancillary proteins could be identified, as well as ion selectivities and voltage dependence for activation/inactivation.

A key example of the contribution of an NC-IUPHAR subcommittee is the orderly naming of the voltage-gated ion channels. Based on a previous consideration of potassium channel nomenclature (Chandy, 1991), Bill Catterall and colleagues identified commonalities of structure of mammalian and non-mammalian channels, sufficient to describe a “chanome” superfamily of voltage-gated ion channels encoded by at least 143 genes in humans. A widely observed feature of the families of voltage-gated ion channels was a selectivity for a single ionic species, with some variation

Home About Targets Ligands Diseases Resources Advanced search Immuno Portal Malaria Portal

Home Targets Ion channels Voltage-gated ion channels Voltage-gated sodium channels (Na<sub>v</sub>)

## Voltage-gated sodium channels (Na<sub>v</sub>)

Unless otherwise stated all data on this page refer to the human proteins. Gene information is provided for human (Hs), mouse (Mm) and rat (Rn).

GtoImmuPdb View OFF Expand all sections Collapse all sections

### Overview

Show » More detailed introduction [GO](#)

### Channels and Subunits

<a href="#">Na<sub>v</sub>1.1 Show summary »</a>	<a href="#">More detailed page <a href="#">GO</a></a>
<a href="#">Na<sub>v</sub>1.2 Show summary »</a>	<a href="#">More detailed page <a href="#">GO</a></a>
<a href="#">Na<sub>v</sub>1.3 Show summary »</a>	<a href="#">More detailed page <a href="#">GO</a></a>
<a href="#">Na<sub>v</sub>1.4 Show summary »</a>	<a href="#">More detailed page <a href="#">GO</a></a>
<a href="#">Na<sub>v</sub>1.5 Show summary »</a>	<a href="#">More detailed page <a href="#">GO</a></a>
<a href="#">Na<sub>v</sub>1.6 Show summary »</a>	<a href="#">More detailed page <a href="#">GO</a></a>
<a href="#">Na<sub>v</sub>1.7 « Hide summary</a>	<a href="#">More detailed page <a href="#">GO</a></a>

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<b>Target Id</b>	584
<b>Nomenclature</b>	<b>Na<sub>v</sub>1.7</b>
<b>Previous and unofficial names</b>	hNE-Na   Nas   PN1   ETHA   NENA   NE-NA   peripheral sodium channel 1   sodium channel protein type 9 subunit alpha   sodium channel, voltage-gated, type IX, alpha subunit   sodium channel, voltage gated, type IX alpha subunit   sodium channel
<b>Genes</b>	SCN9A (Hs), <i>Son9a</i> (Mm), <i>Son9a</i> (Rn)
<b>Ensembl ID</b>	ENSG00000169432 (Hs), ENSMUSG00000075316 (Mm), ENSRNOG00000006639 (Rn)
<b>UniProtKB AC</b>	Q15858 (Hs), Q62205 (Mm), O08562 (Rn)
<b>Sub/family-selective activators</b>	batrachotoxin veratridine
<b>Sub/family-selective channel blockers</b>	tetrodotoxin pIC <sub>50</sub> 7.6 [-100.0 mV] [13] saxitoxin pIC <sub>50</sub> 6.2 [21]
<b>Functional characteristics</b>	Activation V <sub>0,5</sub> = -27 mV. Fast inactivation (0.5 ms)

<a href="#">Na<sub>v</sub>1.8 Show summary »</a>	<a href="#">More detailed page <a href="#">GO</a></a>
<a href="#">Na<sub>v</sub>1.9 Show summary »</a>	<a href="#">More detailed page <a href="#">GO</a></a>

Figure 1. A screengrab of the Na<sub>v</sub> family record from GuidetoPharmacology.org, with the summary view of Na<sub>v</sub>1.7 expanded.

in the mechanisms of endogenous regulation. In a 2003 series of publications in *Pharmacological Reviews*, introduced by Catterall *et al.*, the subcommittee proposed the adoption of a systematic nomenclature naming individual voltage-gated ion channels using the chemical symbol of the principal permeating ion (Na, K or Ca) with the principal physiological regulator

indicated as a subscript. Thus voltage-gated sodium channels have the general description of Na<sub>v</sub>, while calcium-activated potassium channels are described as K<sub>Ca</sub>. A numerical suffix identifies the gene family, while a number following a decimal point defines an individual channel isoform (e.g. Na<sub>v</sub>1.1), where the numbering is organised chronologically.

Many of the targets listed have both summary (Fig.1) and detailed views, where the former enables a more comparative approach and the latter a deep dive into an individual target's properties. On the detailed view of Na<sub>v</sub>1.7 on our database, we identify molecular and biophysical characteristics of the ion channels, linking to a multitude of additional online databases. We focus on

human proteins primarily, with descriptions of mouse and rat orthologues, where these are available. Pharmacological tools listed distinguish activators, inhibitors, gating inhibitors and channel blockers, all with quantitative data, where appropriate, with a major emphasis on the evidence base of the literature. This highlights a second aim of the NC-IUPHAR subcommittees, which is the recognition of preferred tools for target identification. Clearly, we are not yet at the stage when every drug target can be defined by exceptionally selective tool compounds. NC-IUPHAR considered the situation almost 20 years ago - "When using drugs to define receptors or signalling pathways, it would be desirable to use a drug that acts only on the receptor or biological site of interest at all concentrations and doesn't interact with others at any achievable concentration. Unfortunately, there are very few or no drugs with this ideal property. Fortunately, there are numerous drugs with a detectable potency difference (in exceptional cases >10<sup>3</sup>-fold but usually much less) between their primary target and other related receptors." (Neubig *et al.*, 2003). The aim of the Guide is to provide guidance not only for which compound to use to define (as best as is possible) a particular ion channel, receptor, transporter or enzyme in a complex mix, but which concentrations of that agent will be most useful.

GuidetoPharmacology.org provides lists of agonists and antagonists for the receptors, with activators and inhibitors for the enzymes, ion channels and transporters. As of the start of 2022, these aggregate to 3,000 drug targets, with the inclusion of atypical "other" proteins. Lists of the 11,000 ligands are accessible as approved drugs, natural products, metabolites and synthetic organic compounds, as well as endogenous and other peptides, and antibodies. There are nearly 19,000 curated binding constants, with over 31,000 gleaned from large-scale screens and over 41,000 references. Such an abundance of information can be overwhelming, so the Concise Guide to Pharmacology takes a more pragmatic approach. While the online database presents (often very long) lists of information, the Concise Guide has a tabular, comparative approach (Fig.2) with a limited choice of fields and a restricted number of ligands described. It's this approach that makes the Concise Guide concise, not the size of the Guide (the most recent version has 515 pages). The Concise Guide to PHARMACOLOGY 2021/2022 presents ~1,900 drug targets arranged in seven articles focused on ion channels, G protein-coupled receptors, nuclear hormone receptors, catalytic receptors, enzymes,

## Epithelial sodium channel (ENaC)

Ion channels → Ligand-gated ion channels → Epithelial sodium channel (ENaC)

**Overview:** The epithelial sodium channels (ENaC) are located on the apical membrane of epithelial cells in the kidney tubules, lung, respiratory tract, male and female reproductive tracts, sweat and salivary glands, placenta, colon, and some other organs [125, 268, 379, 380, 957]. In these epithelia, Na<sup>+</sup> ions flow from the extracellular fluid into the cytoplasm of epithelial cells via ENaC. The Na<sup>+</sup> ions are then pumped out of the cytoplasm into the interstitial fluid by the Na<sup>+</sup>/K<sup>+</sup> ATPase located on the basolateral membrane [857]. As Na<sup>+</sup> is one of the major electrolytes in the extracellular fluid (ECF), osmolarity change initiated by the Na<sup>+</sup> flow is accompanied by a flow of water accompanying Na<sup>+</sup> ions

[105]. Thus, ENaC has a central role in regulating ECF volume and blood pressure, primarily via its function in the kidney [909]. The expression of ENaC subunits, hence its activity, is regulated by the renin-angiotensin-aldosterone system, and other factors involved in electrolyte homeostasis [536, 909]. In the respiratory tract and female reproductive tract, large segments of the epithelia are composed of multi-ciliated cells. In these cells, ENaC is located along the entire length of the cilia that cover the cell surface [286]. Ciliary location greatly increases ENaC density per cell surface and allows ENaC to serve as a sensitive regulator of osmolarity of the periciliary fluid

throughout the whole depth of the fluid bathing the cilia [286]. In contrast to ENaC, CFTR (ion transporter defective in cystic fibrosis) is located on non-ciliary cell-surface [286]. In the vas deferens segment of the male reproductive tract, the luminal surface is covered by microvilli and stereocilia projections with backbones composed of actin filament bundles [957]. In these cells, both ENaC and the water channel aquaporin AQP9 are localized on these projections and also in the basal and smooth muscle layers [957]. Thus, ENaC function is also essential for the clearance of respiratory airways, transport of germ cells, fertilization, implantation, and cell migration [286, 380].

### Further reading on Epithelial sodium channel (ENaC)

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 Kleyman TR *et al.* (2020) Regulating ENaC's gate. *Am J Physiol Cell Physiol* 318: C150-C162 [PMID:31721612]

Noreng S *et al.* (2020) Molecular principles of assembly, activation, and inhibition in epithelial sodium channel. *Elife* 9: [PMID:32729833]  
 Rossier BC *et al.* (2015) Epithelial sodium transport and its control by aldosterone: the story of an internal environment revisited. *Physiol Rev* 95: 297-340 [PMID:25540145]  
 Sharma S *et al.* (2020) High-resolution imaging of the actin cytoskeleton and epithelial sodium channel, CFTR, and aquaporin-9 localization in the vas deferens. *Mol Reprod Dev* 87: 305-319 [PMID:31950584]

Nomenclature	ENaC <sub>α</sub> βγ
Subunits	ENaC <sub>α</sub> , ENaC <sub>β</sub> , ENaC <sub>γ</sub>
Activators	53969 (pIC <sub>50</sub> 5.9) [645]
Channel blockers	P552-02 (pIC <sub>50</sub> 8.1), benzamil (pIC <sub>50</sub> ~8), amiloride (pIC <sub>50</sub> 6.7-7), triamterene (pIC <sub>50</sub> ~5.3) [126, 510]

### Subunits

Nomenclature	ENaC <sub>α</sub>	ENaC <sub>β</sub>	ENaC <sub>γ</sub>	ENaC <sub>δ</sub>
HGNC, UniProt	SCN1TA, P37088	SCN1TB, P51168	SCN1TG, P51170	SCN1TD, P51172

Figure 2. An extract from The Concise Guide to PHARMACOLOGY 2021/2022: Ion channels (Alexander *et al.*, 2021) focusing on the heterotrimeric epithelial sodium channel, composition and pharmacology.

transporters and other proteins (Alexander *et al.*, 2021). Families of these drug targets are arranged in side-by-side comparisons identifying the preferred nomenclature, links to protein/gene databases, ligands (agonists, antagonists, inhibitors, antibodies) and their characteristics, including affinity/potency estimates, together with general comments. In a divergence from the online database, the priority in the Concise Guide is to feature ligands that are not just selective for the individual target (where appropriate), but are available either commercially or as a gift for researchers to employ.

One of the overarching aims of the Guide and the Concise Guide is to provide an evidence base for researchers to employ. This means that scientists new to a research area can confirm the appropriate compounds and concentrations to employ in complex mixtures to allow identification of individual drug targets. In addition, recommended further reading identifies suitable reviews for researchers to gain a broader contextual understanding. As such, the Concise Guides and the online database at [GuidetoPharmacology.org](http://GuidetoPharmacology.org) provide a valuable resource for the community of physiologists, as well as pharmacologists. For electrophysiologists, in particular, the capacity to compare experimental observations of ion fluxes and drug responses to the information provided on [GuidetoPharmacology.org](http://GuidetoPharmacology.org) should allow rapid identification of a particular channel (or suggest a novel entity). The most recent “point-in-time”, citeable update, The Concise Guide to PHARMACOLOGY 2021/2022 was published in the *British Journal of Pharmacology* in Autumn 2021 and is available online as seven freely downloadable pdfs.

### Maintaining the currency and the quality

One of the features of working in the biological sciences is the pace of change. While experimental protocols and reagents from over a century ago may still be useful in chemistry, for example, the same is rarely true in the biological sciences. A feature of the Guide, and consequently the Concise Guides, is the contemporary nature of the material we present. We have a regular cycle of updates to coincide with the publication of the Concise Guides, where the subcommittees of NC-IUPHAR and other expert consultants provide their reflections on any changes to be incorporated into the database. With this in mind, we are contactable through the database website or via [enquiries@guidetopharmacology.org](mailto:enquiries@guidetopharmacology.org) should you identify an area that you think might be suitable for updating.

## References

Alexander SP *et al.*, (2021). The Concise Guide to PHARMACOLOGY 2021/2022: Introduction and Other Protein Targets. *British Journal of Pharmacology* **178** (Suppl 1), S1–S26. <https://doi.org/10.1111/bph.15537>.

Catterall WA *et al.* (2003). International Union of Pharmacology: Approaches to the nomenclature of voltage-gated ion channels. *Pharmacological Reviews* **55**, 573–574. <https://doi.org/10.1124/pr.55.4.5>.

Chandy KG (1991). Simplified gene nomenclature. *Nature* **352**, 26.

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Vanhoutte *et al.* (1996). X. International Union of Pharmacology recommendations for nomenclature of new receptor subtypes. *Pharmacological Reviews* **48**, 1–2. <https://doi.org/10.1124/pr.114.008862>.

One of the overarching aims of the Guide and the Concise Guide is to provide an evidence base for researchers to employ. This means that scientists new to a research area can confirm the appropriate compounds and concentrations to employ in complex mixtures to allow identification of individual drug targets

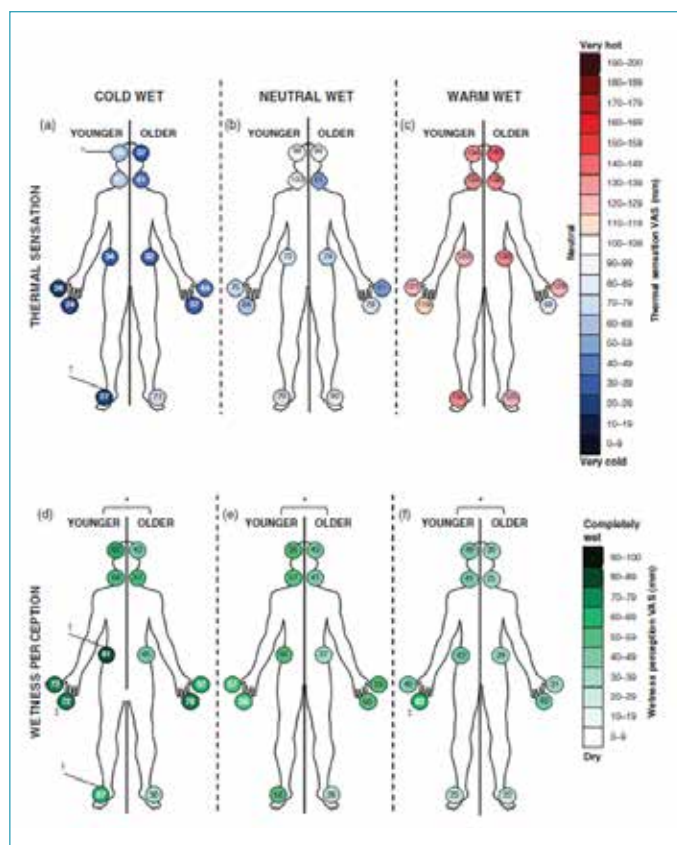
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# EP Experimental Physiology

## Ageing reduces skin wetness sensitivity across the body

Wildgoose C et al. (Oct 2021)  
<https://doi.org/10.1113/EP090027>

Thermal and tactile sensitivity decreases with age. Despite both senses being important for skin wetness perception, whether skin wetness perception changes with age had never been tested. As skin wetness perception impacts thermoregulatory behaviour, determining whether and, if so, to what extent skin wetness perception changes with age could be important information for thermal and comfort needs of elderly individuals. To this end, 10 younger (21–24 years) and 10 older (51–65 years) otherwise healthy male participants of similar heights and weights were exposed to thermal and wetness stimuli at six body locations. Perceptions were recorded on visual analogue scales. Skin conductance was also recorded. The procedure was highly controlled, including time to adapt to lab environment, familiarisation and calibration tests using forearms (site not used during experiment), participant blinding to the stimulus with



Body maps of thermal sensations and wetness perceptions in younger ( $n=10$ ) and older males ( $n=10$ ) resulting from the application of the cold-wet (a,d), neutral-wet (b,e), and warm-wet stimuli (c,f). Numerical data represent group means. Symbols denote statistical differences between regions at  $P < 0.05$ . \*Main effect of age; † interaction age x region, whereby age groups differ at specific body regions; ‡ main effect of body region, whereby index finger pad is different from dorsal foot.

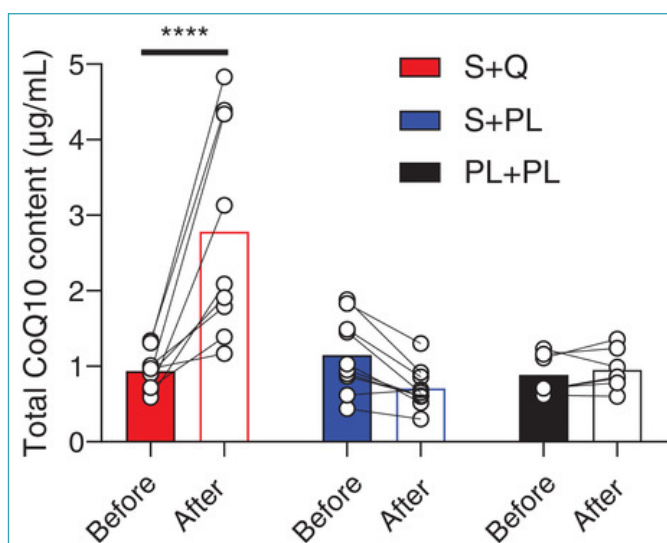
the exception of information about body site, and the counter-balanced orders of exposures between and within participants. Older age impaired skin wetness perception and the extent varied by body site and stimulus temperature (greatest insensitivity for cold-wet on the lower back and dorsal foot). There were few differences in thermal sensitivity, but old age decreased skin conductance; thus, it is likely that decreased skin hydration plays a role in their impaired skin wetness perception. Potential sex differences remain to be investigated.

# JP The Journal of Physiology

## Simvastatin and coenzyme Q10 do not inhibit or augment improvements in aerobic physical capacity in response to training in humans

Kulman C et al. (Feb 2022)  
<https://doi.org/10.1113/JP281475>

Statins are the most widely prescribed cholesterol-lowering drugs in patients with hypercholesterolaemia. They have previously been reported to cause myotoxicity and affect physical performance negatively, while also increasing the risk of new-onset diabetes mellitus. The antioxidant Coenzyme Q10 (CoQ10) may possibly alleviate many of the adverse effects of statins, and in this study, it was investigated whether CoQ10 would antagonise the negative impact of simvastatin treatment on training-induced changes in muscle performance and lipid utilisation during exercise. The investigators found that simvastatin treatment decreased plasma CoQ10, which has previously been proposed as the main mechanism of the alleged myotoxic effects of statins. However, it did not negatively affect the impact of 8 weeks of combined continuous and interval-based aerobic training on exercise performance and substrate utilisation in individuals with hypercholesterolaemia. The results thus lay to rest the idea that simvastatin-treated patients cannot improve exercise performance in response to training, and stress that CoQ10 supplementation presents no further advantages in the adaptations to exercise training in these patients. partnership or their interest in matters of the heart. Indeed, soon after the publication of this paper, Bayliss married Starling's sister, Gertrude.



Plasma concentrations of Coenzyme Q10 (CoQ10) before and after 8 weeks of exercise training + simvastatin + CoQ10 (red), simvastatin + placebo (blue) or only placebo (black) in hypercholesterolaemic patients.



impairment were modest at the age examined, the observed tissue-specific changes may represent early manifestation of age-related inflammatory and metabolic changes. Thus, tissue-specific immunometabolic dysfunction may precede systemic indicators of biological ageing.

## Adipose tissue in active lean older men exhibits pro-inflammatory and metabolic changes

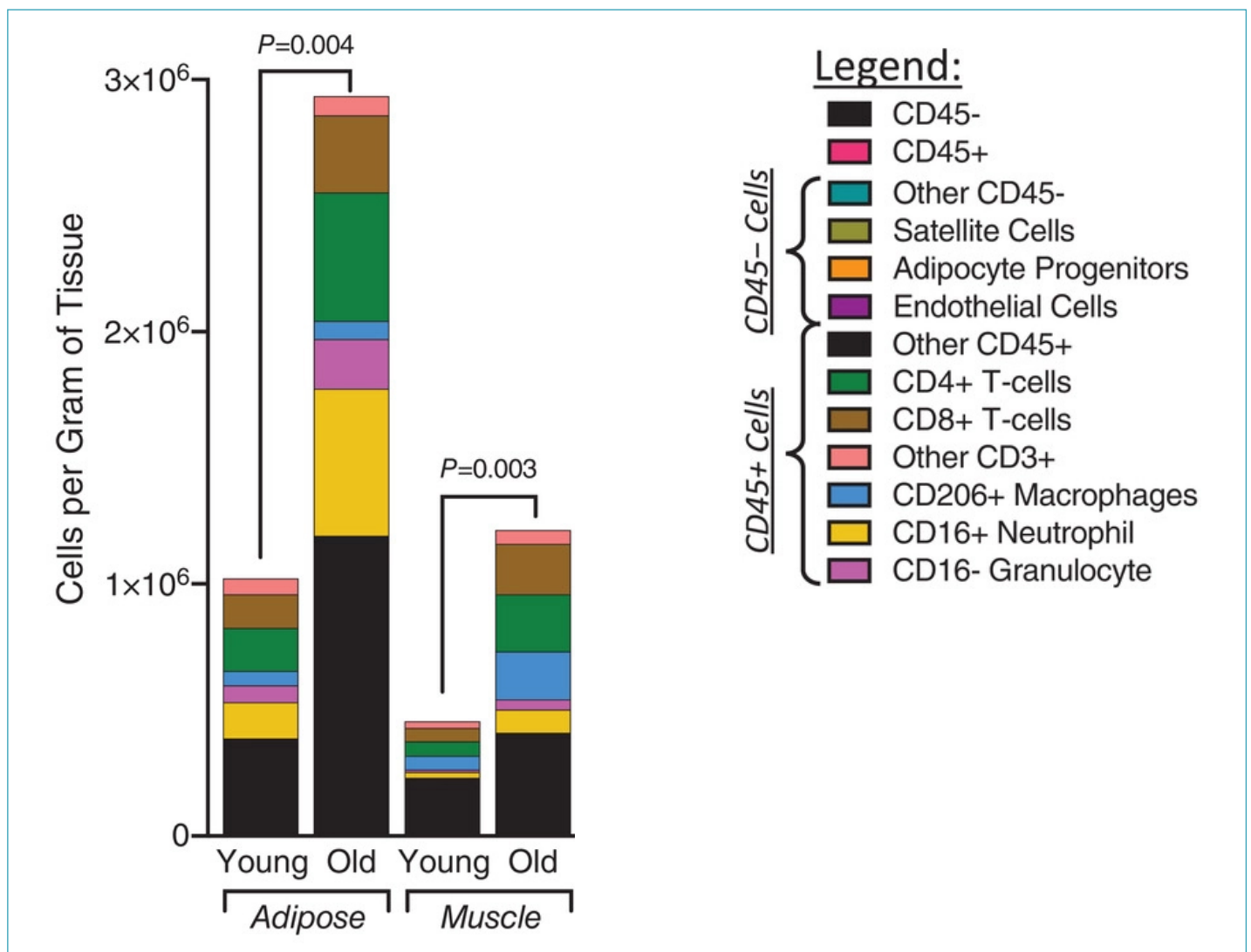
Trim WV et al. (Feb 2022)  
<http://doi.org/10.1113/JP280977>

Low-grade chronic inflammation and deteriorating metabolic health characterise the development of age-associated diseases. The importance of adipose tissue in the regulation of inflammation and metabolic control has been established in obesity, but less is known about the importance of the endocrine functions of adipose tissue in ageing. In this human study, the expression of inflammatory and metabolic proteins in the circulation, skeletal and adipose tissue was characterised in younger ( $27 \pm 4$  years) and older ( $66 \pm 5$  years) lean, physically active male participants. The number of CD4+ and CD8+ T-cells was increased in both skeletal muscle and adipose tissue in the older participants. However, exclusively in adipose tissue, ageing was associated with a striking pro-inflammatory, leukocyte-recruiting secretory phenotype and lower insulin-signalling protein content. As systemic changes in inflammation and metabolic

## Short-term effects on the cardiorespiratory system of a procedure to fix a common cardiac birth defect in infancy

Adrienne R et al. (Nov 2022)  
<https://doi.org/10.14814/phy2.15108>

One of the crucial changes that occurs to the fetal cardiovascular system following birth, is the closure of the ductus arteriosus – the opening between the aorta and pulmonary artery. A patent ductus arteriosus (PDA – i.e. one that remains open) carries significant morbidity for these infants. However, the percutaneous closure of a PDA leads to a rapid change in haemodynamics and can result in hypotension and poor cardiac output. This study analysed indices of myocardial function in a cohort of preterm infants having PDA closure. As well as looking at the effect of closure across the cohort, around 50% of their cohort developed short-term cardiorespiratory instability allowing a comparison between those that did or did not develop instability. The study confirms the changes in left ventricular afterload created by the closure, but also suggests that there may be ways to identify those at risk of complications, which could improve patient care.



Cumulative cell counts per gram of tissue for the CD45+ fraction of adipose tissue and skeletal muscle, between young and old individuals. Young [ $n = 10$  (adipose tissue);  $n = 8$  (muscle)]; old [ $n = 8$  (adipose tissue);  $n = 4$  (muscle)]. All data represent respective group means. Data were analysed using independent samples  $t$  tests or Mann-Whitney  $U$  tests where not normally distributed (Shapiro-Wilks,  $P > 0.05$ ). Trim WV et al. (Feb 2022).



# Physiology 2023

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## Meeting report

### Long COVID: Mechanisms, Risk Factors, and Recovery

*Dr Catherine Hall, Chair of The Society's Conferences Committee, University of Sussex, UK*

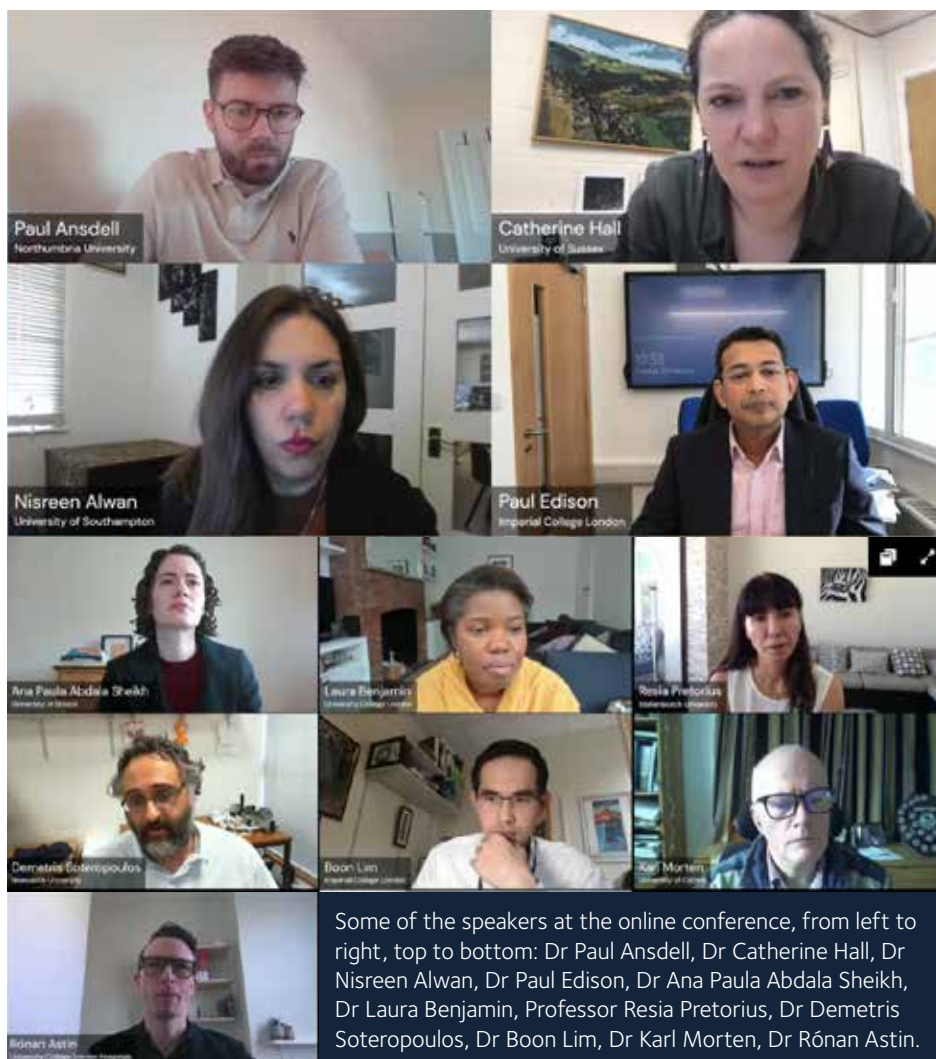
This innovative two-day conference reviewed the challenges of understanding the pathophysiological changes following COVID-19 infection. These persistent symptoms following SARS-CoV-2 infection, otherwise known as "long COVID", have affected people all around the world. It is a heterogeneous disease with multimorbidities and affecting many physiological systems.

Held online from 22-23 February 2022, the conference brought together over 300 physiologists, clinicians, and those affected by long COVID to better understand the underlying mechanisms and identify potential therapies.

The diverse speaker panel addressed topics including characterising long COVID, why some people get it and others don't, the impact of long COVID on active individuals, mechanisms, and the research needed for finding treatments. The conference concluded with a panel discussion on research directions, how to implement this research and how to integrate it with policy. Participants found the two days both innovative and thought-provoking, as the accounts from Laura and Duncan, below, show.

Several speakers commented on the importance of considering the breadth of physiology when trying to work out the characteristics and potential mechanisms underlying long COVID. Many questions remain about the aetiology and optimal therapeutic approach for treating long COVID. Opportunities such as this to try to collectively fit pieces of the puzzle together are likely to be invaluable for shaping future research directions to start to provide much-needed answers.

Society members are reminded that all talks are available to watch on demand on the EventsAIR platform until 31 May 2022. For access, please contact The Society's events team (events@physoc.org).



Some of the speakers at the online conference, from left to right, top to bottom: Dr Paul Ansdell, Dr Catherine Hall, Dr Nisreen Alwan, Dr Paul Edison, Dr Ana Paula Abdala Sheikh, Dr Laura Benjamin, Professor Resia Pretorius, Dr Demetris Soteropoulos, Dr Boon Lim, Dr Karl Morten, Dr Rónan Astin.

#### Dr Duncan Banks

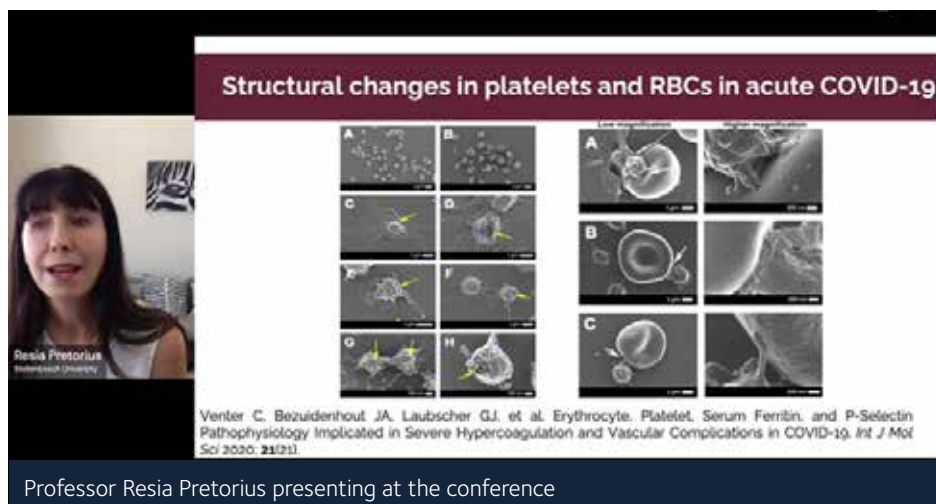
*School of Life, Health and Chemical Sciences, The Open University, UK*

On the first day of the conference, I was fortunate to co-chair the Flash Talk session with my Society colleague Professor Sue Deuchars (University of Leeds, UK). We facilitated eight fascinating presentations that challenged our understanding of the pathophysiological changes that follow COVID-19 infection. The prolonged symptoms of long COVID have affected people throughout the world, are physiologically indiscriminate and target multiple systems leading to a plethora of debilitating symptoms.

Physiologists and clinicians from universities across the UK, the Luxembourg Institute of Health, Federal University of Minas Gerais, Brazil, and Trinity College Dublin described the underlying mechanisms and identified potential therapies for long COVID. A talk by Professor Chris Burton and colleagues suggested that COVID-19

Fascinating presentations challenged our understanding of the pathophysiological changes that follow COVID-19 infection.

affects interoception and that vagal afferent function was disturbed, and that "inaccurate sensing due to disturbed interoception should result in inconsistent patterns of symptoms and relationships with activity". Dr Ahmed El-Medany and colleagues suggested that cardiopulmonary exercise testing could help to progress our understanding of why non-hospitalised individuals with post COVID-19 syndrome have ongoing symptoms. Aurelie Fischer described how her study was



Professor Resia Pretorius presenting at the conference

investigating clinically relevant clusters of people with different forms of long COVID.

According to Clara Carvalho, elite athletes were not spared the ravages of COVID and a return to sports needed to be gradual with medical follow-up recommended.

Similar findings by Rebecca Owen showed that increased physical activity offers no protection against developing long COVID, reinforcing COVID's indiscriminate nature. Dr Roman Romero-Ortuno's talk described how subtle respiratory dysfunction with reduced peak O<sub>2</sub> consumption may contribute to reduced fitness in long COVID, but this may improve over time. Laura Taramova and colleagues used the facilities of the local long COVID clinic to investigate major chronic ailments present with the condition and provide optimal treatments. Comparing the profiles of individuals hospitalised with the virus with those referred to long COVID services, James Yates provided evidence of improved functional status across the board but the extent to which this was observed in long COVID was markedly lower.

**Laura Taramova**

BSc Pharmacology undergraduate student from University of Reading, UK



Long COVID has been characterised by a wide spectrum of symptoms with some of them being fatigue, myalgia, shortness of breath and brain fog. The Physiological Society

brought together researchers, physiologists and wider public individuals to discuss their research and underlying mechanisms of long COVID, its characterisation and prevalence amongst the public as well as potential treatment.

The mechanisms behind long COVID are complicated, however, the speakers were able to collectively compose the bigger picture during the conference. Some aspects of personal interest included cytokine storms, which may persist after the acute phase of COVID-19. Cytokine storms could lead to hypercoagulability, and literature suggests, a higher risk of venous thrombosis.

Presenters also highlighted that long COVID seemed to predominantly affect females, which may be explained by hormonal differences between sexes. This aspect intrigued me as we observed a similar trend during data collection for our study.

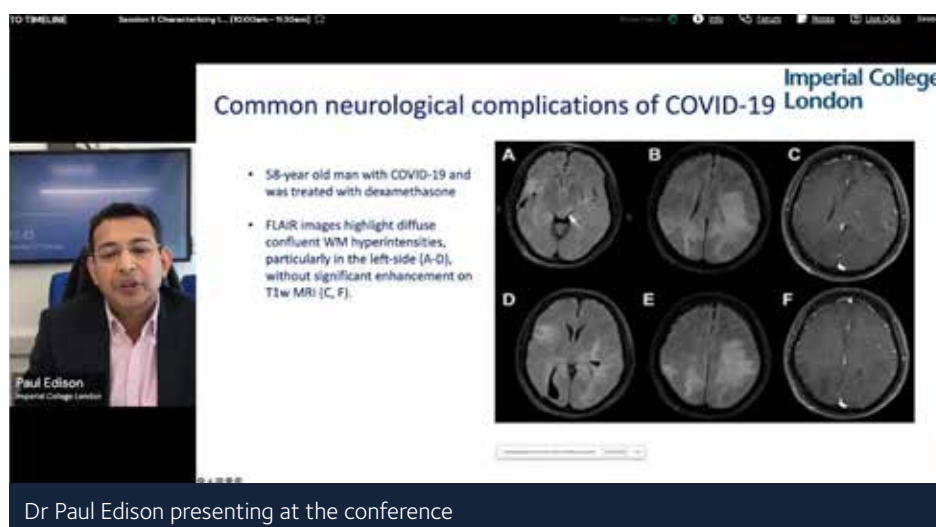
At the Flash Talks sessions, researchers (some of them being from different parts of the world) presented their pilot studies

I was amazed by the variety of studies going on across the world, scientists standing together to explore SARS-CoV-2 and its consequences.

exploring various long COVID aspects. It was particularly interesting to find out that people with higher physical activity levels prior to contracting COVID-19 were not entirely protected from its consequences, as one would have thought.

Therapeutic interventions are under methodical research; nevertheless, there were sessions aimed at potential pharmacological aspects like treatment with monoclonal antibodies. Our team at The University of Reading is also looking at pharmacological management of pain, cardiac, respiratory, and gastrointestinal conditions by collecting questionnaire responses from patients attending post-COVID assessment clinics.

I was amazed by the variety of studies going on across the world, scientists standing together to explore SARS-CoV-2 and its consequences. As an undergraduate student, I was grateful throughout for such an opportunity to listen to brilliant researchers, gain deeper understanding of long COVID and present our own study at the Flash Talks session.



Dr Paul Edison presenting at the conference



## Meeting Preview

### Europhysiology 2022: Let's meet for real

16 –18 September 2022  
Tivoli Congress Centre, Copenhagen,  
Denmark



*Professor William E. Louch  
Chair of Organising Committee and  
Secretary General of the Scandinavian  
Physiological Society, University of  
Oslo, Norway*

*Professor Helle Praetorius  
Chair of Programme Committee and  
President-elect of the Scandinavian  
Physiological Society, Aarhus  
University, Denmark*

For many of us, the COVID-19 pandemic has taken a serious toll. As physiologists, we miss our physical presence in the laboratory, hands-on supervision and, not least, in-person exchanges with our local and international colleagues. Now, as we eye the end of the pandemic, we look forward to rebuilding these connections. With this in mind, we are pleased to announce that Europhysiology 2022 will proceed as an in-person event. Finally, we will be able to meet and share our enthusiasm for physiology with real coffee, biscuits, paper posters, laser pointers, and post-symposium drinks with our new-found collaborators.

Europhysiology 2022 marks the continuation of an ongoing and successful partnership between The Physiological Society, The Scandinavian Physiological Society, The German Physiological Society, and the Federation of European Physiological Societies. This series of meetings kicked off in London in 2018, with a dynamic congress that was widely praised by attendees. Set in beautiful Copenhagen, this year's meeting promises to continue this tradition. We are proud to present a high-calibre and diverse scientific programme featuring world-class invited lecturers and symposia. The structure of the meeting will also give ample opportunity to showcase attendees' research with over 100 slots for oral communications and poster sessions placed centrally in the meeting programme.

To complement the main meeting, Europhysiology will be supplemented with a pre-meeting programme. This will importantly

include a Young Physiologists' symposium focused on scientific career building, and critical themes for early career physiologists. For those craving greater insight into their favourite areas of physiology, the pre-meeting programme also includes seven thematic meetings in the fields of neuroscience, skeletal muscle, cardiac, vascular, renal, comparative, and human and exercise physiology. We often hear from our colleagues that these smaller, focused meetings provide an excellent opportunity for scientific networking.

Science aside, a great argument for attending Europhysiology 2022 is Copenhagen itself! As the cosmopolitan capital of Denmark, *København* never disappoints. Our local organising committee has cut no corners in delivering an optimal meeting setting, which is sure to facilitate engagement and interaction in a cosy atmosphere. Indeed, the entire programme is set within walking distance of the conference centre, with easy access to Copenhagen living, bicycles, cafés, a creative melting pot of classical and modern architecture and, of course, Danish design. To top it off, the conference dinner will take place in Tivoli Gardens, one of the oldest amusement parks in the world, known for its ambience, concerts, excellent dining and artistic fireworks.

We look forward to welcoming you all, whatever your career stage, in Copenhagen at Europhysiology 2022. Let's meet for real!

Find the programme and registration details at [europhysiology2022.org](https://europhysiology2022.org)

## Meeting Preview

## Processing and Modulation of Sensory Signals: From the Periphery to the Cortex

20 – 21 June 2022  
The Royal College of Physicians,  
London, UK

*Dr Jamie Johnston,  
University of Leeds, UK*

*Professor Jennifer Linden,  
University College London, UK*

*Professor Susan Deuchars,  
University of Leeds, UK*

We are delighted to announce that after two postponements due to the pandemic, this 2-day, in-person conference will now take place in London in June 2022. This meeting will be a fantastic opportunity to come together to talk about an essential topic – how we sense the world around us and how we convert sensory signals into information and action. The breadth of this topic gives us a chance to hear from a diverse programme of speakers, discussing sensory signals in different modalities and at different levels – from peripheral transduction to cortical integration – which we hope will make for a unique and unmissable conference!

The conference will be delivered in four sessions: peripheral and brainstem processing; thalamic and cortical processing; sensation, location and action; and modulation of the senses. Each session will see invited speakers giving 25-minute talks with time for questions. In addition, we also have a session for Flash Talks – 3-minute research summaries – chosen from submitted abstracts, as well as a new and innovative session “speed dating of techniques”. These events will give attendees the opportunity to learn from and share techniques with each other, with the aim of fostering new connections and ideas across modalities and levels of sensory systems research.

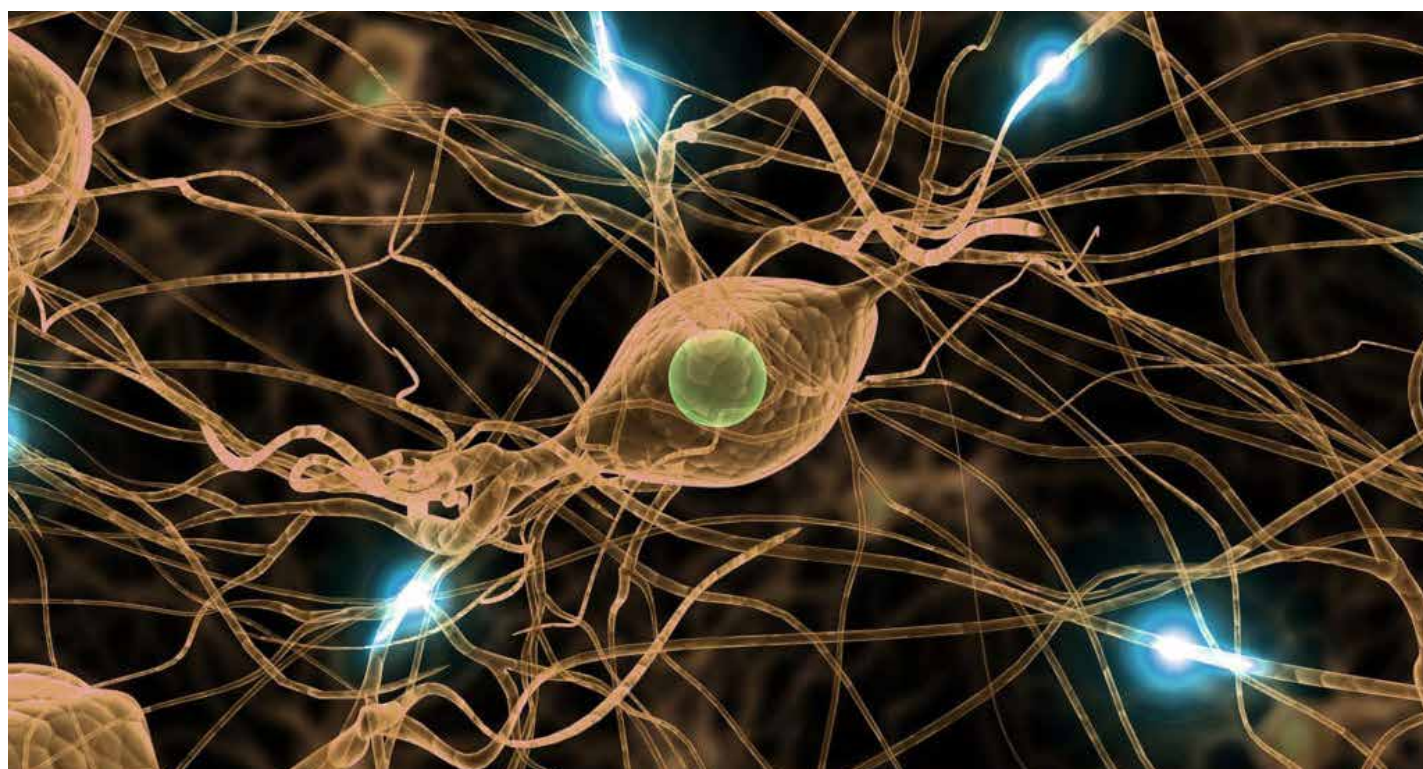
In addition to the scientific programme, we hope to be able to offer a great social programme that will allow researchers to network and cross-pollinate ideas while catching up with friends and colleagues. The conference will take place at the Royal College



of Physicians, which is opposite London's beautiful Regent's Park. Sadly, we cannot guarantee sunny weather in the UK in June, but we can guarantee a fantastic and inspiring conference, and we hope that you will join us!

### Key dates

- 4 February** – Registration opens
- 1 – 31 March** – Abstract submission
- 30 April** – Early registration closes
- 6 June** – Registration deadline
- 20 – 21 June** – Conference



## Congratulating our 2021 Honorary Fellows

Following their formal announcement at the 2021 President's Lecture and Award Ceremony, which was held at The Royal Society in London in November, the Board is delighted to announce our seven 2021 Honorary Fellows of The Society.

*Professor Dame Kay  
Davies, CBE DBE  
FMedSci FRS*



Kay Davies is Professor of Genetics and co-Director of the Muscular Dystrophy UK Oxford Neuromuscular Centre at the University of Oxford, UK. Professor Davies' research interests lie in the molecular analysis and development of treatments for human genetic diseases. She has published more than 400 papers, won numerous awards for her work and co-founded companies to translate her work to the clinic. In 2008 she was made Dame Commander of the British Empire for services to science.

*Professor Maria  
Fitzgerald, FMedSci  
FRS*

Maria Fitzgerald is Professor of Developmental Neurobiology at University College London, UK. Internationally recognised, her work has had a major impact on our understanding of how pain perception emerges in childhood and how early pain experience can shape pain sensitivity for life. She has received many honours, awards and fellowships.



*Professor Christine Holt,  
FRSB FMedSci FRS*



Christine Holt is Professor of Developmental Neuroscience at University of Cambridge, UK, where her laboratory studies how nerve connections are first established in the brain. Holt has been the recipient of numerous grant awards, fellowships and prize medals, including the António Champalimaud Vision Award.

*Professor Carla J. Shatz  
PhD ForMemRS*

Carla Shatz is Professor of Biology and Neurobiology at Stanford University, US, where she is also Director of Stanford Bio-X, an interdisciplinary biosciences institute. Professor Shatz's research aims to understand how early developing brain circuits are transformed into adult connections during critical periods of development. She has received many awards in her career, including the Gerard Prize, the Gruber Prize, the António Champalimaud Vision Award, the Kavli Prize in Neuroscience and the Harvey Prize in Science and Technology.





*Professor Fiona Watt FRS  
FMedSci*

Credit: Martin Phelps



Fiona Watt is the Director of the European Molecular Biology Organization having recently stepped down as Executive Chair of the Medical Research Council. She is internationally recognised for her work on stem cells and their interactions with the niche in healthy and diseased skin. Watt has received fellowships from many notable organisations and has been the recipient of many awards throughout her career.

*Professor Melanie Welham  
FRSB*

Melanie Welham is Executive Director of Science at the Biotechnology and Biological Sciences Research Council, the largest public funder of non-medical biological research in the UK – investing around £450 million annually. Prior to taking up this role, Welham was Professor of Molecular Signalling at the University of Bath, UK, where she developed a career as a leading researcher in molecular signalling and stem cell science. She was the first female professor appointed in the 97-year history of her department and served as Co-Director of the University's Centre for Regenerative Medicine for 4 years.



*Rt Hon. Lord David  
Willetts FRS*



David Willetts is the President of the Resolution Foundation, an independent think-tank focused on improving living standards. From 1992 to 2015, Willetts served as the Member of Parliament for Havant and was the Minister for Universities and Science from 2010 to 2014. Willetts is a Visiting Professor at King's College London, a Board member of UK Research and Innovation and Chair of The Foundation for Science and Technology.

You can find out more about all our Honorary Fellows at  
[physoc.org/honorary-fellows/](https://physoc.org/honorary-fellows/)

## Nominate an Honorary Fellow

Do you know an exceptional scientist who has contributed to the advancement of physiology?

► [physoc.org/honorary-fellows-nomination-form/](https://physoc.org/honorary-fellows-nomination-form/)



## Physiology Friday 2021

Every year, we celebrate Physiology Friday and call on our members to hold exciting outreach activities to help showcase the amazing world of human and animal bodies. Physiology Friday 2021 once again saw members around the world engaging their communities in a wide range of fun and engaging ways. Here we share a few of the reports from members about their Physiology Friday celebrations.

### Kuban State University of Education, Sport and Tourism, Russia

This year, all the staff and postgraduates of our Department of Physiology participated in the preparation for the celebration of Physiology Friday with incredible enthusiasm.

On 12 November 2021, we held the Science Festival *Physiology in our Life* at the University, in a blended format. Events included a photo exhibition from our Physiology Friday celebrations in 2019, physiological testing stations, a quiz, games and debates, including *Drugs in Sports*.

A public lecture *Physiology in our life: Contemporary Problems and Prospects* was held online at the regional conference on Sports Medicine by Associate Professor Irina Shvydchenko.

We would like to express our gratitude to The Physiological Society for funding this event, which seeds the growth of future successes in promoting physiology.

### University of Glasgow, UK

Lecturer in Physiology Dr Ian Rowe set up a special stall in the University cloisters to engage staff, students and the wider public on Physiology Friday.

Physiological Society-funded projects by the School of Life Sciences' Miss Marie Bowers and Dr Craig Daly were showcased as well as a demonstration of green bicycle power by Dr Greig Logan.

"That's pure bonkers..." was the take from one visitor on entering the virtual reality of physiology as built by Craig as part of his project.

The cloistered calm of the University of Glasgow at the end of COP26 was witness to the potential of the "plug and play" biosensors from AD Instruments.

This activity also underlined the importance of structure and function in physiology, with Greig's cyclist calves commented upon by at least one observant passer-by.

Global warming is real – but hadn't quite reached us in the cold cloisters. The warmth of positivity towards Marie Bowers and her "Science Travels" outreach project for Gypsy, Traveller, Roma, Showmen and Boaters, however, was clear to all.

Dr Rowe said: "Huge thank you to my fabulous colleagues Marie, Greig, Craig, Katherine Price and Shona McQuilken for putting on a great event in the cloisters and making it a pure, dead brilliant Physiology Friday."

### University of Benin, Nigeria

Physiologists at the University of Benin graced Physiology Friday with so much excitement as it gave us a sense of belonging and value in the system. Also, students of the department illuminated the campus with their massive turnout and excitement.

The outreach campaign was divided into two parts:

1. Physiologists visited some secondary schools the day before, to raise awareness in the younger minds between the ages 15–25, on who a physiologist is and physiology's role in society.
2. Outreach was carried out in the University, where we had the attention of different levels of students, from the freshmen to final year and the general public. They were enlightened on the significance of the "Physiologist in our society" and encouraged to study physiology as a major.

We had the presence of top physiologists including the dean of the faculty, who presented wonderful lectures and left everyone excited and hopeful.

### University of Ibadan, Nigeria

It was a day like no other. The turnout from the students was massive and their interest in learning about physiology was mind-blowing. The day was packed with activities that got the message across to the students, including a public lecture and an outdoor physiological workshop, both aiming to:

- Raise awareness and understanding of physiology as a discipline among secondary

school students, and the opportunities it brings.

- Raise awareness of secondary school students on their body physiology and appreciation of the same.

Over 500 students attended and the guest speakers for the public lecture and the team of facilitators for the workshop did a wonderful job.

Many of the students even went ahead to register with UIPSA (University of Ibadan Physiology Student's Association), indicating their interest to be followed up on how they can get started in physiology, as a career and a discipline.

Many of the students asked us to come back next year; however, there are a lot of other highly populated schools that we desire to reach with the good news of physiology as a discipline and a career.

### King's College London (KCL), UK

In celebration of Physiology Friday 2021, the KCL Physiology Society, The Physiological Society and Promega collaborated in hosting a physiology-inspired art competition at King's College London.

The idea of our event was to interest students in physiology and teach them through colouring and drawing. Participants had to come up with an experiment and turn it into art.

Some students decided to study the effect of cycling on the quality of drawing or show the difference in drawing with their right and left hands. Other students were inspired by the anatomical models provided by the University. Every piece of art was awarded with freshly baked brownies. The winners of our art competition were given Nando's gift cards.

Our Physiology Friday event was a big success. We involved both societies, Promega, students and University staff in a creative way and we are very grateful to The Physiological Society and Promega for the funding and supporting our ideas.

In addition to the art event, we interviewed lecturers in physiology at King's College London and asked them about their favourite physiology facts and inspirations. The interviews can be found on our Instagram (@kclphysiologysociety) and Twitter (@kcl\_physysoc).

Many thanks to Dr James Clark, Tanyel Ashik, Maya Wilson and Margot Jacobs for their involvement and help with organising the event.



Students being weighed during the physiology workshop in Ibadan, Nigeria



Some of the artworks completed in the Physiology Friday competition at KCL, UK



Blood pressure measurements overseen by keen students in Ibadan, Nigeria



Some of the team at the KCL stand



A visitor tries out the virtual reality tour of physiology, in Glasgow, UK



Measuring blood oxygenation in Kuban, Russia



Dr Greig Logan demonstrating green bicycle power in Glasgow, UK



Lots of people were involved in celebrations at the University of Benin, Nigeria

## Welcome to our new Theme Leads

*The Physiological Society's seven Themes enable members to access like-minded networks where they can discuss their latest findings and forge new collaborations.*

The main academic coordinators of the seven Themes are known as Theme Leads. They are an essential focal point for members, help to promote the Theme activities, and encourage members and non-members to participate in Society events.

Each Theme focuses on a different area of physiological research, and within them are 23 overlapping specialities. When presenting research at Society events, members can align their abstracts or presentations according to both a Theme and a speciality.

The Society recently appointed seven new Theme Leads, who join the existing Theme Leads and their counterpart Early Career Theme Leads. Each incoming Theme Lead was chosen due to their passion for physiology and their wish to provide relevant, topical symposia and meetings to advance their Theme.

The new Theme Leads introduce themselves here. They are working with the Conferences Committee to shape future events, and would love to hear your ideas – you can reach them by emailing [events@physoc.org](mailto:events@physoc.org).

More information on the Themes and Theme Leads can be found at [physoc.org/join/themes/](https://physoc.org/join/themes/)

### Cardiac & Vascular Physiology

*Dr Cathal Breen*

*Senior Lecturer in Physiology & HCPC-registered Clinical Scientist, Ulster University, UK*



*Credit: Ulster University, UK*

I aspire to bridge links between The Society and clinical physiology and healthcare scientist practitioners I educate in my role as senior clinical academic. This will provide a body for these cohorts to align to, to provide support to The Society ventures and to provide research submissions. I will bring energy, enthusiasm, and innovation to this role within The Society to galvanise membership contributions and dissemination of Society endeavours.

*Dr Kamalan Jeevaratnam*

*Associate Dean International (FHMS) & Reader in Clinical Physiology, University of Surrey, UK*



As Theme Lead, I am keen to embrace and promote the concept of One Health-One Medicine in physiological sciences and also hope to promote the interaction between data science and fundamental physiological research through interdisciplinary events and meetings. In addition, as a person of colour I am keen to champion diversity and inclusivity in physiological teaching and research. The COVID-19 pandemic has shown how physiological parameters can vary between people of colour and Caucasians and that this gap in our understanding requires the attention of the physiology community.

### Endocrinology

*Professor Sanjit Dey*

*Professor of Physiology, University of Calcutta, India*



My major goal as a Theme Lead is to uphold endocrinology as a flagship research area in my continent in particular. We need to modernise the scientific teaching, both in theory as well as at the bench, so they satisfy the demands of the healthcare issues. Metabolic disorders are in an epidemic stage in Indian society. It requires a concerted action and awareness among the common masses. I will extend the advocacy of The Physiological Society to students, researchers, colleagues and scientists from academic and research institutes and include them actively in this initiative. My research in cell signalling, the role of antioxidants in cellular stress management, and metabolic disorders complement my role in the endocrinology Theme.

## Dr Gareth Nye

Lecturer in Physiology & BMedSci  
Medical Science Programme Lead,  
University of Chester, UK



I am extremely excited to take up this role and move the presence of endocrinology within The Society forward. Endocrinology forms a major part of both my personal and professional life. My research interests concern pregnancy physiology, maternal and fetal health and the development of health and disease. Within this, I have interests in placental biology. Personally, having a daughter with type 1 diabetes means I am fully aware of the intricacies of endocrinology care. With my connections within the Society of Endocrinology, I believe I can truly expand the provision of endocrinology within The Physiological Society and look forward to meeting many current and future members.

## Epithelia & Membrane Transport

### Dr Stephen Keely

Senior Lecturer in Pharmacy and  
Biomolecular Sciences, Royal College of  
Surgeons in Ireland, Republic of Ireland



The Physiological Society, and in particular the Epithelia & Membrane Transport (EMT) section, have been an important focal point for myself and my research group since I arrived at RCSI in 2005. I, and my students,

have had the opportunity to showcase our research, organise symposia in areas of high research interest, and get to know some of the finest physiologists in our field of study. I have benefited immensely from the work of Theme Leads that have gone before me and as Theme Lead myself, I hope to give something back to the section by helping to ensure that current and future generations of physiologists enjoy the same benefits as I did. Working with the other EMT Theme Leads, I hope that we can build on the current strengths to maintain and grow our engagement.

## Human, Environmental & Exercise Physiology

### Dr Paul Ansdell

Lecturer in Exercise Physiology,  
Northumbria University, UK

The Human, Environmental & Exercise Physiology Theme encompasses a wide range of topics across the spectrum of health and disease, from mechanistic studies investigating the acute responses and long-term adaptation to exercise, to the optimisation of physical function in a variety of populations. Indeed, it is the study of how physiological systems integrate to determine physiological function that attracted me to this Theme, and my aim is to highlight the importance of human physiology and promote the work of physiologists within our Theme. Along with the other Theme Leads and colleagues in The Physiological Society, we hope to achieve this through conferences, symposia, workshops,

and other professional development opportunities.

## Dr Irene Di Giulio

Lecturer in Anatomy and Bio-  
mechanics, King's College London, UK

I believe that this Theme has a fundamental



role in science and in public society. I aim to support other members and showcase the role of physiology with the public. Specifically, I have two main goals. One is to foster scientific advancement and support scientists in an inclusive environment. The second is to engage with the public to show the importance of physiological research for the health-span and for tackling the major current global challenges.

## Our existing Theme Leads, who remain in post until 2023:

**Professor Chris Garland**  
University of Oxford, UK  
(Cardiac & Vascular Physiology)

**Professor Mike Althaus**  
Bonn-Rhein-Sieg University of  
Applied Sciences, Germany  
(Epithelia & Membrane Transport)

**Professor Andrew Murray**  
University of Cambridge, UK  
(Metabolic Physiology)

**Dr Paul Meakin**  
University of Leeds, UK  
(Metabolic Physiology)

**Professor Charlotte Stagg**  
University of Oxford, UK  
(Neuroscience)

## Obituary: Professor John Finlay Benzie Morrison (1942–2021)



Professor John Finlay Benzie Morrison

John Morrison, Emeritus Professor of Physiology at the University of Leeds, UK, died on 24 September 2021, aged 79, following the diagnosis of soft tissue sarcoma in 2018. He read medicine at the University of Edinburgh, the city of his birth, and during his undergraduate career revealed early leanings towards medical science, with prizes at the 2nd Bachelor of Medicine examinations in Anatomy, Biochemistry and Physiology, and an intercalated honours degree in Physiology in 1963. After graduation in medicine MB ChB in 1966, he spent a year doing medicine and paediatric surgery at the Western General Hospital, Edinburgh. In 1967 he was awarded an MRC Junior Research Fellowship, and while undertaking some locum GP work, and clinical assistantships in Clinical Neurophysiology, he worked on the effects of gonadal hormones and polypeptides on the nerves of the vascular system under the supervision of Professor Mary Pickford FRS, FRSE. During his thesis research he learnt the MJ Purves method for recording carotid body flow from Tim Biscoe, and the Iggo and Voigt method for extracellular recording from single active fibres from Alan Brown. In 1970 he was awarded his PhD and appointed as a Lecturer in the Department of Physiology at Leeds.

He established his mammalian neurophysiology laboratory, initially with recordings from single active fibres in single visceral afferents, whose projections were followed onto spinal cord interneurons using microelectrodes, and thus to sympathetic reflexes. This was at a time when workshop-made, custom-designed analogue recording electronic kit was being supplemented and replaced by manufactured digital systems. His research was mainly concerned with the spinal afferent innervation of viscera, and the influences these nerves have on autonomic and somatic functions, and in particular the lower urinary tract. He was promoted to Senior Lecturer in 1976, Reader in 1983 and to a personal chair in 1988. During this period, he was convenor of the Autonomic Special Interest Group of The Physiological Society. His publications include two books. The first, a volume on *Visceral Sensation* within the *Progress in Brain Research* series, was edited jointly with Fernando Cervero (Cervero & Morrison, 1986); the other, with Michael Torrens, on the *Physiology of the Lower Urinary Tract* (Torrens & Morrison, 1987), remains a landmark publication in this field.

Postgraduate and postdoctoral researchers trained in his laboratory have developed careers in physiology and medical research and became professors or consultants. John was particularly proud when Stephen McMahon (1954–2021), who completed his PhD in 1979, and moved on to a postdoctoral fellowship in Pat Wall's laboratory, was appointed Sherrington Professor at King's College London in 1996.

In 1986 John was awarded the Mahalanobis gold medal of the Indian Physiological Society. In 1992 he was awarded an FRCS(Ed) (ad hom) for his work on human pathophysiology, which involved collaborations with surgeons and physicians in Leeds and London. He was a Visiting Professor at the Tokyo Metropolitan Institute of Gerontology on three occasions in the 1990s, was awarded a medal by the Akita Medical Society in 1995, and elected a Fellow of the Institute of Biology in 1996.

He was Head of the Department of Physiology in Leeds from 1987 to 1992, and during his tenure of the Headship, the research and teaching profiles of the department were enhanced. Numbers of staff, postgraduate students, fellows, grant income and publications all increased, as research infrastructure moved from individual laboratories towards shared facilities. As student numbers increased, undergraduate teaching evolved, with the recruitment of teaching assistants and the introduction of computerised learning technology. During this expansion and reorganisation, John remained a very supportive and kindly colleague, encouraging and developing the careers of staff and students, while extending his research from physiology into pathophysiology. Sadly in 1989 his wife, Lynn, who had been his lynchpin since his time in Edinburgh, died of breast cancer.

In 1997, he decided to take early retirement from Leeds and was appointed as Professor and Chair of Physiology at the United Arab Emirates (UAE) University in Al Ain. As well as a busy teaching and administrative schedule, he continued research in both neuro-urology, and diabetic neuropathy. He was also involved in a long-term project that resulted in the translation into English of Trendelenburg's seminal German paper from 1917 (Lammers *et al.*, 2006). He actively promoted research both within the UAE University, through mentoring and committees, as well as in the UAE at

large: chairing the Awards Committee of the Sheikh Hamdan Medical Foundation, John was much more than a dedicated and respected scientist and teacher.

In 2000 he married Dr Kath Rayfield, a former colleague from Leeds, and they enjoyed a happy family life with his two stepchildren and four grandchildren. During their time in the Middle East, they also became involved with higher education establishments in neighbouring countries, and travelled widely, enjoying the local foods, mountains and deserts. On their return to the UK, John was awarded emeritus status by the University of Leeds in 2008.

In his youth, John played violin, piano and organ, and was Dux in Music at Dunfermline High School in 1959. During his retirement he took up the violin and piano again and became a member of the Sinfonia of Leeds in 2011, regularly playing in their concerts. His involvement in music and travel was limited following the diagnosis of sarcoma in 2018, and he began to use his iPad for art. He continued to be intellectually engaged in physiology, and

his last published paper (Morrison *et al.*, 2019) was a Royal Society biographical memoir on his thesis supervisor, Mary Pickford.

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Written by Professor William Winlow, University of Liverpool, UK and Professor Arun V Holden, University of Leeds, UK

John remained a very supportive and kindly colleague, encouraging and developing the careers of staff and students

# Environmental Impacts on Pregnancy and Offspring Outcomes: Lessons Learned and Avenues for Intervention

29 September 2022  
Coin Street Conference Centre, London, UK

This symposium will bring together researchers studying different model systems to help improve our understanding of pregnancy and life course physiology.



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Abstract submission

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