PN
Physiology News

Issue 122/ Summer 2021

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Preparing for the Olympics and beyond

The Physiological Society

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Welcome to the Summer 2021 edition of *Physiology News*

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Cover image: 3D reconstructed confocal image viewed along the inside of a mouse muscle fibre segment showing multiple nuclei towards the cell periphery. Image by Einar Eftestøl, University of Oslo, Norway.

YOUR ONLINE MEMBER COMMUNITY

LAUNCHES THIS SUMMER!

Join physiologists from across the world to discuss, learn and share ideas using our new online Member Area.

- **Build supportive relationships** and grow your network with physiologists across career stages and interests
- **Develop your career** through member-only professional development webinars and resources
- **Expand the reach of your research** with our lively, global community
- **Continue the conversation** beyond our conferences and webinars
- **Share your ideas and explore new approaches** to research and teaching in a friendly, supportive environment

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The Physiological Society

A Summer Issue to hopefully take with you on holiday

Dr Keith Siew

Scientific Editor, *Physiology News*

Julia Turan

Managing Editor, *Physiology News*

Welcome to another issue of *Physiology News*. Hopefully as this arrives in your pigeonhole (or inbox for those of you reading this online), you will be enjoying the first days of summer. For many of us, last summer was our first bit of respite from the socially distanced "new normal". What came with it was a strange new quietness to suburban life, a sky devoid of the roar of jet planes overhead or constant hum of traffic, the air itself smelled sweeter.

And it may seem like an eon ago, but as the world approached 2020, global warming was set to be top of the world's agenda. Be it in the wake of the UN Climate Action Summit, when our children took to the streets in the first global climate strike, or after the young Greta Thunberg made an indelible mark on us all with her powerful COP25 speech. Eventually it became all but impossible to ignore with the images of hellish infernos emblazoned across our screens, the Southern hemisphere itself from the Amazon to the Australian Bush seemingly ablaze. That was until the world stopped.

The temporary lull in activity due to the pandemic led to one of the most significant drops in air pollution in modern history. And while this brought glimmers of hope to those in the fight against climate change, the health implications for many were more profound. In the short term it was estimated that around 24,200 premature deaths had been avoided between February and March in China alone, and in the long term, a potential 300,000 additional deaths may be averted across China and Europe combined[1]. And as life slowly returns to normal, flights resume and with more cars on the road, Abigail Whitehouse's expert discussion of the types of air pollution we encounter in urban life and the pathophysiology that underlies the deterioration in health many face couldn't be more timely (p. 30).

Come summer 2021, with the continued vaccine rollouts across the world, the relief we all feel will hopefully be more enduring this time round. Many large events with little to no social distancing are set to return, and perhaps none more anticipated than the postponed Summer Olympic Games set to go ahead (at the time of writing) in Tokyo, Japan. If you're one of those rare few athletes, or those of us lucky enough to travel for holidays in the coming months, it will no doubt be a jarring experience to once again traverse time zones. And in this issue of *PN*, our Editorial Board's own Dr Philip Lewis along with Professor Thomas Erren have composed a guide to tackling jet lag for your convenience (see p. 22).

In addition to keeping your chronobiology in sync, those undertaking endurance exercise and working up a sweat may want to keep their acid–base balance in check[2]. For the reader in search of a new perspective on an old dilemma, we invite you to read the essay by Dr Jon-Emile Kenny on the virtues of the Stewart Model of acid–base balance (see p. 26), which is garnering support among those who deal with physiology more acutely in the clinical realm.

Alternatively, you may also want to look at some dietary hacks to improve your performance, and the team of authors at Anglia Ruskin University have you covered, with an article on the surprising properties of various juices and concentrates from your five-a-day (see p. 18). For the more controversial, we also have a piece on hacking your physiology with Eftestøl and Bruusgaard discussing the long-lasting cellular memory and epigenetic effects of exogenous hormones like testosterone and erythropoietin (see p. 34).

Lastly, this issue would not be complete without acknowledging the centenary of the discovery of insulin. One of the biggest breakthroughs in medical history that revolutionised the treatment of diabetes and brought about a revolution in hormone replacement therapies in the decades that followed. Although, like most discoveries, things were not so straightforward or without strife, and the new chair of The Physiological Society's History and Archives Group, Professor Angus Brown, delves into the drama surrounding the perfect storm of insulin's discovery and how it could have so easily gone wrong (see p. 14).

We hope you enjoy this issue and have a wonderful summer.

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Professor David Paterson

President, The Physiological Society

Placing physiology and physiologists at the centre of key discussions about research, innovation, and funding

A few weeks ago we received the welcome news that the UK Government had averted threatened cuts to UK science funding following vocal opposition by The Physiological Society and organisations across the scientific and higher education spectrum.

At the end of 2020 it was announced that the Brexit deal, the Trade and Cooperation Agreement, would enable the UK to associate with Horizon Europe, the world's largest research programme. This is very welcome and will ensure continued collaboration between UK and European researchers.

When the UK was an EU member state, involvement in European research programmes was funded as part of the UK's membership fee. Post-Brexit, the UK will have to pay this association fee separately. There was growing concern that existing research funding could be cut by over £1 billion in 2021/22 to pay for it. This is the cost of funding the entire Medical Research Council and Science and Technology Facilities Council combined, and equivalent to cutting more than 18,000 full-time academic research posts.

Thankfully, days before the start of the new financial year, the Government announced additional funding to meet the costs this year. However, there remains uncertainty about how these costs will be met in future years.

The Government has gone ahead with planned £120 million cuts to Official Development Assistance funding. This has left many universities facing difficult decisions, reducing their ability to collaborate with international partners and constraining the UK's role in combatting the world's most pressing challenges.

Science is a global endeavour and the UK needs to pay close attention to the funding landscape elsewhere in the world.

The Organisation for Economic Co-operation and Development (OECD) average is for 2.4% of GDP to be spent on R&D, with South Korea spending 4.6% of GDP, Germany 3.2% and Japan 3.1%. The US spends 3.1% and President Biden has unveiled a historic $325 billion research and innovation plan. In comparison, total R&D expenditure in the UK was 1.7% of GDP (2018). The Government has reaffirmed its commitment to increase UK R&D funding to 2.4% of GDP by 2027 – that is welcome, but still only the OECD average despite aspirations for the UK to be a "science superpower".

Outside of Government, the pandemic has resulted in research charities being forced to make big cuts in spending. For example, Cancer Research UK has had to cut its research funding by £45 million. This is around half of what the charity would normally expect to be spending at this time, and it means dozens of potential life-saving projects and hundreds of world-class scientists have been left unfunded.

With scientists rapidly decoding the mystery of COVID-19, providing new treatments and, ultimately, allowing the world to return to normality through vaccines, the public benefit of long-term investment in R&D is now clear to all. We must therefore hold politicians and decision makers to their funding promises, to ensure the resources are in place to develop the science base we need for the future.

This latest funding scare shows that, while this Government has made welcome commitments, The Physiological Society must stand ready with organisations across our sector to make our case.

In this instance, we were ready to move quickly and I wrote to the Prime Minister, along with President-Elect Professor David Attwell, and CEO Dariel Burdass, to express our concerns.

As the economy recovers from the pandemic, we must continue to focus on raising the visibility of the discipline of physiology and make the case for its role in advancing knowledge, improving health and delivering on public priorities.

That is why across 2021 we are delivering a series of projects designed to raise the profile of the discipline across three core areas: knowledge translation, research and teaching.

In January we launched our report into knowledge exchange, *Translating Knowledge and Research into Impact*, in collaboration with the National Centre for Universities and Business. We brought physiologists together with industry, through AstraZeneca and GlaxoSmithKline, research institutes, knowledge exchange professionals and higher education bodies to highlight the important role of physiology research to knowledge exchange activities. The report, launched with Professor Melanie Welham, Executive Chair of Biotechnology and Biological Sciences Research Council (BBSRC), has led to a wide-ranging programme of activity of conferences, professional development resources and mini projects focused on Scotland, Wales and Northern Ireland.

Ahead of a planned review by Government into the Research Excellence Framework (REF), we have initiated a project considering how REF can best support interdisciplinary research. This builds on a roundtable we held with the Campaign for Science and Engineering in January.

On teaching, we are working in partnership with the Academy of Healthcare Science on a thought-leading report on the economic benefits of the study of physiology to students and to the wider UK economy.

These projects place physiology at the centre of key discussions about research, innovation, and funding. Alongside these, 2021 will also see the launch of our blue plaques highlighting distinguished physiologists.

This combination of pride in our heritage and ambition for the future will raise the visibility of physiology among institutions, government and students in the months and years to come.

Our members are the bedrock of all these activities – thank you for your support, which enables us to build a world where physiology flourishes.

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Dariel Burdass

Chief Executive,
The Physiological Society

The importance of community

Communities are an essential part of society, bringing people together around a shared interest. The Physiological Society is committed to empowering an inclusive and diverse community of members with networking opportunities and the skills required to fulfil their potential in a global economy.

Being part of The Physiological Society and its smaller communities is beneficial as it offers a space for collaboration, connection, networking, and friendships to occur. Being a "broad church", our door is open to all physiologists, supporting members across all stages of their careers. We want members to come with us on a journey by providing an enhanced membership experience, to ensure The Society remains relevant, as they nurture their interest and career in physiology.

The strategic importance of inclusivity and community was highlighted at our event on 16 April with diversity advocate and physiologist, Dr Oz Ismail, as we took the first step to creating our Diversity and Inclusion Roadmap for Change. Oz is a research scientist and co-founder of the Minorities in STEM network, which helps support and showcase ethnic minorities in science. He is also passionate about raising LGBTQ+ voices both within science and within ethnic minority groups. Oz shared his experience, spoke about his advocacy work and about why it is important for organisations such as ours to commit resources to being an open and inclusive society.

We recognise that we are at the early stage of a long-term piece of work to ensure we reflect the communities we serve and are inclusive of all cultures, experiences, and identities as this will strengthen The Society and the discipline. Listening to our members will provide us with the qualitative evidence to support the data that already highlights the need for change. The event in April was the first of many opportunities that members and non-members of the physiology community will have to share their own experiences. Please do take time to join in and help The Society make positive changes on inclusion by sharing your views. Making your voice heard will help inform our Roadmap for Change and the more members that respond, the better we can understand your needs.

While we have not been able to meet physically since the pandemic began, we have sought ways to bring our community together virtually through our online meetings, networking opportunities and professional development activities.

As we plan our post-pandemic "new normal", it seems certain that there will be a greater demand for members from across the UK and around the world to keep connected virtually. We have invested in a bespoke online membership platform and are excited to be launching our new online Member Area, featuring our online Member Community.

The Member Area will be accessed via our website and each member will have their own member homepage. A benefit of the Member Community is that it is fully integrated with our website, so every member automatically has an account, and it simply requires the same login credentials as is used to book an event or apply for a grant.

We are developing engaging new member-only resources, such as professional development advice and guides. Members will also be able to access a growing library of webinars and member-only content. By continuing to provide training and skills-based opportunities for physiologists, to enable them to take advantage of new technologies and the developments arising from them, this will enhance the membership experience.

Our Member Community will enable members to communicate wherever they are in the world about topics related to physiology and The Society, as well as their research and teaching. This will offer a space to foster inter-member learning as members can share their experiences and debate the best solutions to common problems. This will also help The Society assess what members are interested in, so we can better tailor our member offering.

The Member Area and Member Community are due to launch this summer. Over the coming weeks and months, we hope to build a thriving online community of physiologists and look forward to hearing your feedback.

Based on the report's findings, a series of recommendations have been made for the UK Government, institutions and The Society, aimed at maximising the contribution of physiology and addressing knowledge exchange barriers.

"We have invested in a bespoke online membership platform and are excited to be launching our new online Member Area, featuring our online Member Community."

Please do contact me to let me know what we do well, where we could do better, what we might stop doing and what we could do more of.

Our summer round of recruitment is now open. You will have received more information via email for positions on various committees, and also the Editorial Board of this magazine which closes on 4 July.

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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

November 2020
The Board of Trustees met virtually on 26 November 2020. The Chair welcomed the new Trustees: President-Elect Professor David Attwell, Chair of Education, Public Engagement and Policy Committee Dr Lucy Green, and Early Career Trustee Dr Daniel Brayson.

The President presented his Road Map for 2021, which was to increase the visibility of both The Society and the discipline through a series of Member Roadshows, which he hoped could be held in person during 2021.

It was noted that the Roadshows would focus on the following themes:

- Networking with like-minded individuals and being part of a community
- Why being part of The Society matters
- The benefits of being a member of The Society
- How to get more involved with The Society

The CEO began her report with the positive news that The Society was named as one of four finalists in an Association of Association Executives award recognising support to members during COVID-19. The CEO felt this showcased the work that had been done during COVID-19 by staff, Trustees, and the membership. The Society subsequently went on to win this award.

The Honorary Treasurer updated Trustees that the 2020 budget showed a saving on the expenditure side of around 20% due to the cancellation of face-to-face activities. He added that income was steady with a slight downward revision in the forecast of publication income from Wiley. He stated The Society was looking at a healthy surplus for 2020 in combination with the investment portfolio having recovered the losses of spring and being in a slight surplus due to the vaccine news. The Board also approved the 2021 budget.

The Honorary Treasurer informed Trustees that a small group had been formed to review The Society's investment strategy. The group, with the help of external consultants, planned to review The Society's Investment Policy Statement to include an ethical policy statement.

Following a recommendation from Nominations Committee, Trustees agreed to appoint Professor Paul McLoughlin (Chair of Publications) and Dr Catherine Hall (Chair of Conferences) taking up their roles at the Member Forum in November 2020.

Trustees approved a new grants programme proposal, which has three elements to it:

1. Conference Attendance Awards
2. Institutional Engagement Awards
3. Professional Development Awards.

The programme of support was built to develop advocates for The Society and to improve member engagement, enabling members to see a clear pathway of membership progression. In addition, the programme supports long-term sustainability of The Society through financial resilience. The President formally thanked Professor Prem Kumar, the Chair of the Grants Review Task and Finish Group, and his team.

The President welcomed the Editor-in-Chief (EiC) of *Journal of Physiology* (*JP*), Kim Barrett, and EiC of *Experimental Physiology* (*EP*), Mike Tipton, to the meeting. Both EiCs gave presentations that highlighted the challenges and opportunities for each of the journals as well as the high-level picture for the future for their journals. The President thanked both EiCs for their presentations and for the hard work they put into The Society journals as the public face of science for The Society.

Finance Committee

November 2020
The Committee received and discussed the third-quarter Management Accounts and reforecast narrative. The revised October 2020 forecast showed an operating surplus; however, updated figures from Wiley showed publishing income was down based on a more cautious 2021 forecast. The Committee discussed and approved the 2021 budget to take to the Board, the product of the Senior Management Team's (SMT) work with committees and chairs to strategically look at what they wanted to deliver in each of their areas during 2021.

The CEO stated that the budget-setting process would occur earlier in 2021 and be defined by the strategic direction set by the Board. The Committee discussed putting the 2020 surplus in a designated COVID response fund to use against the extra cost of running hybrid events and webinars in 2021 for the short term, with the Board needing to discuss the longer-term strategy for events beyond 2021.

The Committee was updated on the planning meeting with the new auditors, Buzzacott, where the audit approach and logistics were discussed.

The Ethical Review on Investment working group gave an update on their first meeting about a new Investment Policy Statement with consideration of environmental, social and governance factors.

The CEO introduced the upcoming planned property review and requested volunteers for a Property Strategy working group to help review the modelling. Dr Kamalan Jeevaratnam, a Reader in Clinical Physiology at the University of Surrey, was recommended as a new member of the Committee following a successful interview. Two departing committee members, Dr Phil Aaronson and Professor Bridget Lumb, were thanked for their important and valuable contributions.

Conferences Committee

April 2021
The spring 2021 meeting of Conferences Committee was once again held online on 16 April, chaired by Dr Sue Deuchars, University of Leeds, UK. The Committee welcomed Dr Catherine Hall, the incoming Chair of Conferences Committee, who also attended.

The meeting first discussed the landscape of Society conferences in a post-COVID world and how these can offer value to members and encourage new members to join. Although mooted as the ideal format for meetings going forward, a true hybrid conference did not seem the best solution for

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the membership. The preferred option was that the smaller meetings should be a mix of in-person and online conferences, particularly as air travel may be prohibitive for some and online provides a more environmentally sustainable option. The committee also discussed ways of engaging with researchers who may not see themselves as physiologists by having reciprocal symposia at other societies' conferences.

Following the success of the joint online conference with the Intensive Care Society, the committee agreed to take forward an online conference for 2022 on multimorbidity, for an audience of physiologists and clinicians.

The longer-term future of The Society's annual conferences was also discussed and recommendations made. Following Europhysiology 2022, the next Annual Conference will be Physiology 2023, in July 2023. The venue has yet to be decided but it was felt that this would be an in-person event, with aspects that could be provided virtually.

The meeting reviewed the conferences programme for late 2021 and 2022, which includes the following:

- *Regeneration Across the Systems: Translational Opportunities for Novel Therapeutic Avenues* (Edinburgh, 14 – 15 December 2021). This meeting was postponed from December 2020 and it is hoped will be our first in-person event since 2019.
- *Processing and Modulation of Sensory Signals: From the Periphery to the Cortex* (Royal College of Physicians, 20 – 21 June 2022). This was originally planned for June 2020.
- *Biomedical Basis of Elite Performance 2022* (University of Nottingham, April or December 2022). The venue had confirmed that this could be run as a hybrid meeting.
- *Future Physiology 2022* (dates and venue TBC).

www.physoc.org/about-us/board-of-trustees/committees-and-groups/

"Trustees approved a new grants programme proposal, which... was built to develop advocates for The Society and to improve member engagement."

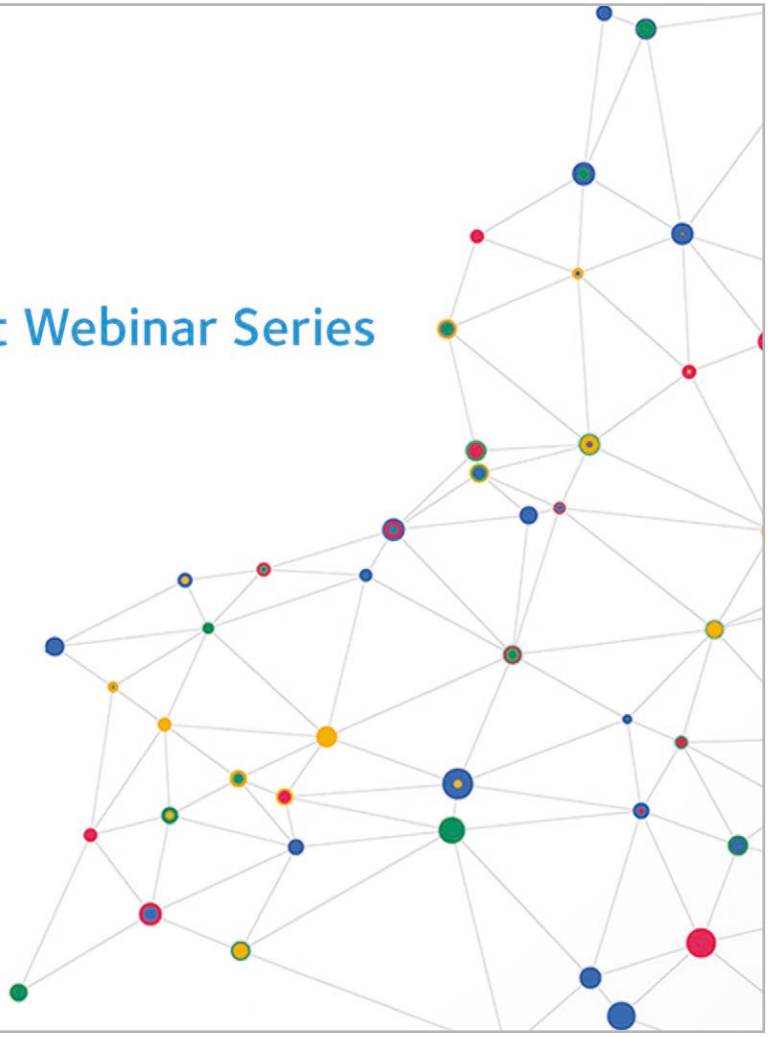
The Physiological Society

Professional Development Webinar Series

Research Impact: Why it Matters for Your Career
Friday 11 June 2021 I 14:00 - 15:00 BST

Building Successful Partnerships between Research and Industry
Tuesday 15 June 2021 I 13:00 - 14:00 BST

Using Online Tools to Identify New Research Opportunities
Friday 18 June 2021 I 13:00 - 14:00 BST



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The Society's *In Vivo* Taskforce

Professor Lucy Donaldson
University of Nottingham, UK

Professor Andrew Trafford
University of Manchester, UK

The Society's *in vivo* taskforce held its first meeting of 2021 back in March, an opportunity to reflect on the work of the previous 12 months and to identify emerging challenges and opportunities to those members who use animals in research.

The historians among the membership will know that The Society's foundation back in 1876 was in response to a Royal Commission that recommended the introduction of the Cruelty to Animals Act 1876. This stood until it was replaced by the current statute, which regulates the use of animals in research, the Animals (Scientific Procedures) Act 1986 (ASPA). As such, The Society's longest standing area of policy interest relates directly to the work of the current taskforce.

Last year was a busy one with the UK's withdrawal from the European Union coinciding with the impact of COVID-19 on access to laboratories and ensuring the welfare of animals during lockdowns, furlough schemes and restricted travel. As the UK Government has transposed more general EU laws and regulations on animals (such as the transportation of pets and livestock) into UK law, a number of opportunities for misunderstanding about the standing of animals in research in relation to these areas have arisen and The Society's taskforce has worked closely with the Royal Society of Biology (RSB) to ensure that civil servants are aware of the nature of this work and that transpositions to UK law also account for existing regulation for animals used in research.

While much of The Society's influencing in this area is done in collaboration with the RSB, Understanding Animal Research (UAR), The British Pharmacological Society (BPS), and the NC3Rs, the *in vivo* taskforce ensures that issues that disproportionately affect physiologists are kept firmly on the agenda and that the voice of physiology is represented on funders' and policy makers' working and stakeholder groups.

One clear example of the group's continuing work is the ongoing BBSRC nationwide survey into the "use of models in research". While the online survey was first made publicly available in June 2020, the *in vivo* taskforce was consulted as part of the development of the survey and members of the group have been co-opted onto the working group responsible for analysing its results.

One of the taskforce's main focuses for this year is understanding how the shift towards online teaching of *in vivo* courses, as a result of COVID-19, will affect the granting of future educational licences by Animal Welfare Ethical Review Bodies (AWERBs). We will work closely with other learned societies such as BPS and RSB and other key stakeholders to better understand the impact of the move to online teaching on the educational experience and any implications this move has on the operation of ASPA for educational purposes.

Finally, for the past 18 months, The Society's *in vivo* taskforce has been working with the BPS on the Research Animal Sciences Education Scheme (RASES). This collaborative project is to support dissemination and delivery of the BPS' *Curriculum for the use of research animals* to institutions who run relevant BSc or MSci/MSc biosciences programmes. This is to ensure that as many bioscience undergraduates and postgraduates have access to high-quality animal research training and education as possible.

As such, *in vivo* policy remains a central part of The Society's work as the taskforce seeks to address the challenges that members face. As highlighted above, there are a number of projects currently ongoing and the taskforce would encourage members who work with animals in any manner to engage with our work to ensure it remains as responsive as possible.

If you would like to raise specific issues related to *in vivo* policy or are happy to be contacted by the taskforce in future, please contact **taddison@physoc.org.**

Read more about the Research Animal Science Education Scheme on our blog and in the British Pharmacological Society's magazine:

physoc.org/blog/free-support-scheme-for-educators-to-improve-students-understanding-of-animal-research/

bps.ac.uk/publishing/pharmacology-matters/march-2021/introducing-the-research-animal-sciences-education

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The Rights Retention Strategy – what is it and why does it matter?

Simon Rallison

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Professor Deborah Baines

Chair of Publications Committee, The Physiological Society & St. George's University of London, UK

Alex Stewart

Deputy Managing Editor, *Experimental Physiology*, UK

The Rights Retention Strategy (RRS). If you're a researcher you'll probably be hearing more about it, but what is it? Take a deep breath. This isn't simple.

In September 2020 cOAlition S made a significant change to its Plan S by adding to it the Rights Retention Strategy.[1,2] Readers of *PN* will be familiar with Plan S as an initiative from a group of European research funders aimed at accelerating the transition of journals from subscription or hybrid models to Open Access (OA).[3]

Up to that point Plan S had been pushing authors in the direction of Gold OA. With Gold OA, the journal publishes the copy-edited, typeset and proofread Version of Record (VoR) of an article and makes it freely accessible with liberal re-use licensing. In return for this publishing service, they are paid by the author, funder, institution or sponsor.

The RRS instead offers an alternative route to author compliance with Plan S, through posting a copy of the author's accepted manuscript (AAM) in an open repository (so-called Green OA) for access *without embargo* (so immediately on publication in the journal) and with the same Creative Commons (CC) BY reuse licence as is used for Gold OA.

The instrument the cOAlition S funders have used to open up this route is to change their grant conditions to require that a CC BY licence is applied to all AAMs or VoRs reporting original research, supported in whole or in part by their funding.

The differences between this route and Gold OA are that the AAM is a more preliminary version of the paper and that the journal receives no payment for the article becoming OA. Publishers are concerned that the RRS raises a real risk that if enough of a journal's content is made free to access and reuse through the AAM/RRS route, libraries will cancel their subscriptions, undermining the journal's financial viability at a critical point during the transition to the promised land of Gold OA.

Many societies and publishers, while committed to a transition to OA, feel that the RRS is a blunt instrument and risks collateral damage to journals, like The Society's *Journal of Physiology* (*JP*) and *Experimental Physiology* (*EP*), that are already on a clear path to Gold OA. They also think it could lead to an inferior, last-resort version of OA based on the AAM.[4] Perhaps unsurprisingly, both parties in the debate claim to be defending the author's right to choose where to publish.

That said, few authors submitting to *JP* and *EP* are likely to have to resort to the RRS (The Society's *Physiological Reports* was born OA so complies with all funder mandates, everywhere). Phew!

Through Wiley's read-and-publish agreements our journals comply with Plan S's OA mandates in most of the countries where the cOAlition S funders are active (in the UK, primarily Wellcome Trust and UK Research and Innovation). For instance, UK universities are covered by the agreement Wiley signed with Jisc last year, and the 10 institutions belonging to the IReL (Irish Research eLibrary) consortium in Ireland are covered by a four-year agreement finalised in March. Wiley also has read-and-publish deals with consortia of academic libraries in Germany, Italy, The Netherlands, Austria, Hungary, Sweden, Norway and Finland, and with a handful of individual institutions in the US. Authors in institutions covered by read-and-publish deals have a straightforward and, to the author, cost-free route to publishing fully Gold OA (Version of Record, freely accessible, no embargo, CC-BY licence) in *JP* and *EP*.

If you're thinking of submitting a paper to *JP* or *EP* (and we hope you are) on research supported by a cOAlition S funder you can confirm compliance with Plan S by using its clever Journal Checker Tool for your combination of journal, institution and funder.[5]

The option of Gold OA in our journals is a substantial benefit to authors in terms of wider dissemination and citation.

The endgame for Plan S is that from January 2025 research supported by the participating funders should be published in fully OA journals. Read-and-publish deals are an important step along that path, in allowing authors to comply with their funders' mandates during the transition and while bedding in new flows of funds within the funder–library–publisher system.

There are still plenty of other issues to be addressed, particularly around ensuring publishing equity for authors and the financial impact on learned societies reliant on their journal income, which is likely to take a hit.

It's also important to note that OA is only one branch of the Open Science Movement and that The Society's journals have made steps along other branches, which are arguably more impactful.[6] For example, both *JP* and *EP* have started awarding Open Science Badges as an incentive in a bid to increase data availability, while *EP* recently published one of the first Registered Reports in physiology, outlining the journal's commitment to combatting publishing biases. Moving forward, a form of Open Peer Review may also be on the horizon, as we look to ensure our journals remain at the forefront of best scientific publishing practices. It's quite a journey, and we will keep members informed as we continue on it.

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Exercised: The Science of Physical Activity, Rest and Health
By Professor Daniel Lieberman

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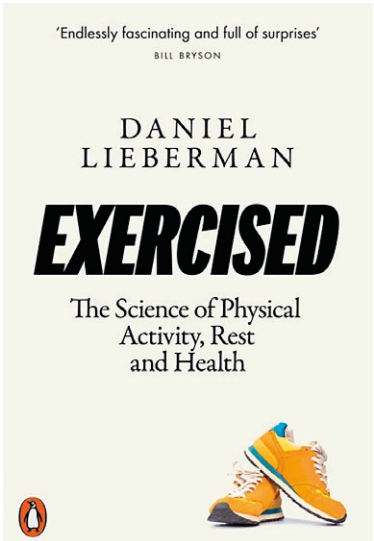

Daniel Lieberman, Penguin (2021)
ISBN: 9780141986364

"Now what?"

Having hauled itself away, the train no longer shields them from the wind. Standing on the platform, their shivering eyes follow the grim heath beyond them. In the distance, a rocky prominence, solitary beneath a silvery Scottish sky.

"We go for a walk," says Tommy casually.

"What?" asks Spud.

"A walk," Tommy says again. "There." And pointing across the rugged scene, he sets off to tread the land, to climb the hill.

His friends follow, hesitant. But no sooner have they crossed the tracks than they stop, shaking their heads.

"Well, what are you waiting for?"

Spud swigs his Special Brew. "Tommy." How to put it? "This is not natural, man."

Bewildered, Tommy gasps, "It's the great outdoors! It's fresh air!"

No use. Spud, Renton, and Sick Boy are not convinced. Turning, they go back the way they came, accompanied by a disappointed Tommy.

An amusing moment. One among many in Danny Boyle's *Trainspotting*. And one, I suspect, that another Daniel would have little difficulty comprehending.

Professor Daniel Lieberman reveals a lot about himself in his intriguing new book. Making my way through *Exercised* (I read every page, a courtesy rarely shown to writers by their readers, not to mention their reviewers) gave me the sense of becoming better acquainted with its author. I'm confident, therefore, that Professor Lieberman would empathise with the boys in *Trainspotting*. Professor Lieberman is an enthusiastic exerciser – he's run marathons (plural), for fun. So, it's easy to imagine him hiking the Scottish Highlands with Tommy. An eminent biologist, Professor Lieberman would disagree with Spud's judgement of the great outdoors as "not natural." But he would regard Spud's reluctance to walk in it as perfectly normal. Why? Because he thinks humans didn't evolve to exercise.

At the outset, Professor Lieberman distinguishes "exercise" from "physical activity." Since few people read novels, let alone dictionaries, he generously gives definitions.

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Physical activity (noun): any bodily movement produced by skeletal muscles that expends energy

Exercise (noun): voluntary physical activity that is planned, structured, repetitive, and undertaken to sustain or improve health and fitness

In his view, "we never evolved to exercise – that is, do optional physical activity for the sake of health and fitness." Rather, humans evolved "to be physically active when necessary."

While it's true that the word "exercise" is a noun, it's also a verb. I assume, since no evidence is offered to the contrary, that the biology of exercising muscles, process and outcome, is the same regardless of whether the action is voluntary or involuntary.

Professor Lieberman seems willing to ignore this, however, as he shifts ground throughout his book. On the one hand, he makes the persuasive case that the ancestors of *Homo sapiens* were naturally selected for their ability to travel over great distances, walking and running across Africa and beyond. That is to say: they, and hence we, evolved the anatomy and physiology needed to exercise their muscles and move their bodies.

On the other hand, Professor Lieberman rigidly affirms that we didn't evolve to exercise. Savanna, yes. Spin class, no. Insisting upon a distinction between "physical activity" and "exercise" seems to me to be as helpful as asserting that our ears evolved to hear gorillas but not to listen to *Gorillaz* (I refrain from opining upon which is more grating).

It's a not-so-slight sleight of hand that, at best, disorientates the reader and, at worst, confuses what is otherwise clear writing.

Professor Lieberman is most comfortable (find me an academic who isn't) when explaining his own research. At the book's core is the juxtaposition of so-called WEIRD societies (Western, educated, industrialised, rich, democratic) with traditional hunter-gatherer populations. Synthesising knowledge from years of fieldwork in Africa and Mexico, he contrasts how people in disparate cultures engage in exercise (or should that be physical activity?), the effects this has on their bodies, and the consequences for health and disease. The comparisons are revealing.

"Sedentary Westerners spend as much daily energy walking as chimpanzees, but hunter-gatherers like the Hadza walk about three times more than an average Westerner, spending nearly twice as many calories despite weighing much less... hunter-gatherers spend about 10 percent of their total energy budget trudging about, but Westerners spend only 4 percent... if average industrialized people walked as much as the Hadza, they would spend approximately 350 calories a day walking. If they didn't compensate for all those spent calories by eating more, they would slowly but surely shed pounds."

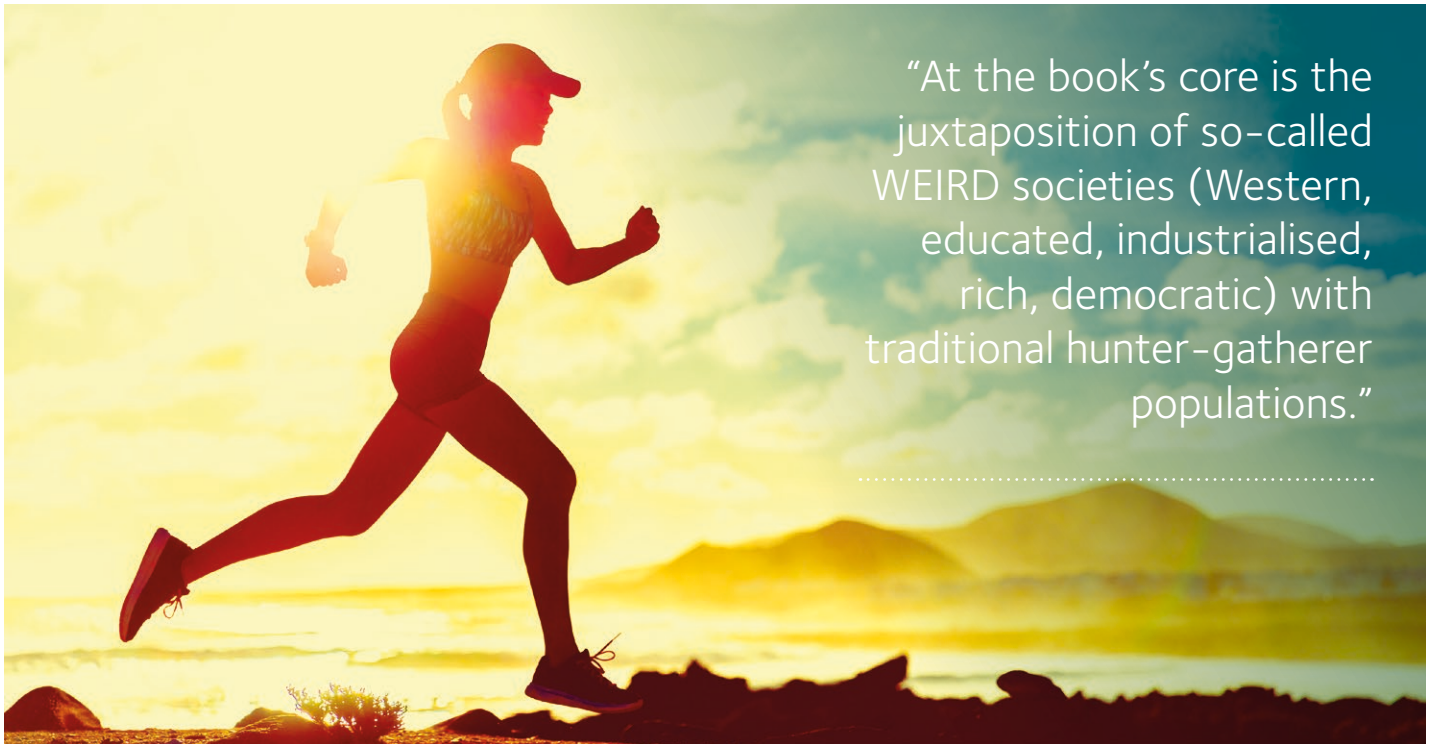
Whether or not one agrees that the separation of "exercise" from "physical activity" is redundant, Professor Lieberman's concern that we don't do enough of either is valid. Obesity, for instance, continues to attain new epidemic heights, supplementing other chronic diseases. (I would offer WEIRDO as a more suitable acronym, but it's becoming increasingly visible that obesity is the one trait the West is willing to share with the developing world.)

I found Professor Lieberman's blend of anthropology, evolutionary biology, and physiology pleasing enough. There is a fair amount of popular science writing intended, I would imagine, for the general curious reader. Mitochondria are introduced as the "tiny power plants in cells," a marginal improvement on the ubiquitous and tiresome use of "powerhouse." The inelegant word "behooves" is invoked too readily, and Professor Lieberman possesses that American peculiarity of placing question marks where they have no business being. Yet in other respects, the prose is coherent if conventional.

Professor Lieberman would like to avoid having *Exercised* branded a support manual: "this is not a self-help book." And yet, part of the book's charm comes from the sensitive manner with which he encourages his reader: "we should treat exercise the way we treat education by making it fun, social, emotionally worthwhile, and something that we willingly commit ourselves to do." My fear, though, is that the audience most likely to read this amicable book (young, educated, well-off, healthy) is least likely to require its recommendations. Then again, one could do worse than to reacquaint oneself with decent advice.

Make exercise necessary and fun. Do mostly cardio, but also some weights. Some is better than none. Keep it up as you age.

Now what? We go for a walk.



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One hundred years of insulin

An alternative history

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We are approaching the centenary of the discovery of insulin, the greatest medical breakthrough of its time. It elevated Sir Frederick Banting to the status of national hero, honoured with countless awards including a knighthood and a Nobel Prize. To this day Banting remains the youngest Nobel Laureate in Physiology or Medicine, receiving the Prize in 1923 at 32 years of age.

Prior to the discovery of insulin, a diagnosis of type 1 diabetes was a death sentence. Patients were typically pre-pubescent children presenting with weight loss, excessive thirst, hunger and glucosurea. The only effective treatment was a calorie-restricted diet that starved the body of carbohydrates that fuelled the hyperglycaemia and coma that inevitably preceded death. Intensive research in the three decades preceding Banting's work identified the islets of Langerhans in the pancreas as the source of the internal secretion believed to regulate blood glucose. Several research groups had demonstrated the ability of crude extracts of pancreas to reduce glucosurea in diabetic dogs, but the side effects resulting from impurities in the extract precluded progression to clinical trials.

Insulin was discovered at the University of Toronto, Canada, by a group of four researchers: Frederick Banting (1891 – 1941), John Macleod (1876 – 1935), Professor Charles Best (1899 – 1978) and Professor James Collip (1892 – 1965) (see Figure 1). Banting, although trained as a surgeon, was intrigued by the role of the internal secretion of the pancreas in the development of diabetes mellitus. He proposed to Macleod, Professor of Physiology at the University of Toronto, the idea of ligating the pancreatic ducts in dogs in an attempt to destroy the acinar cells that produce the digestive enzymes (the external secretion), suspected of destroying the internal secretion. The atrophied pancreas, which should be devoid of external secretion while retaining the internal secretion, would be grafted into another dog rendered diabetic by total pancreatectomy and the urine glucose measured to test the effectiveness of the graft.

Macleod, an expert on carbohydrate metabolism, was attracted to Banting's skills as a surgeon, clearly a considerable asset when applied to grafting. Macleod supplied Banting with a laboratory, dogs, and an assistant, undergraduate student Charles Best. The promising results of the early experiments encouraged Macleod to extend funding, and to recruit biochemist James Collip to oversee the successful purification of the internal secretion, which MacLeod named insulin from the Latin, insula, meaning island, referring to the pancreatic islets.

But it could all have been so different (Table 1).

Discovery vs. invention

A discovery is a lesser achievement than an invention, the former requiring a "find" of an existing entity, whereas the latter requires creation. Inventions are considered the pinnacle of scientific achievement, since they originate in the imagination of an individual(s), without whose insight they would not exist,

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THE TORONTO DAILY STAR

30TH YEAR. TWENTY-EIGHT PAGES. TORONTO, WEDNESDAY, MARCH 22, 1922. 5 O'CLOCK EDITION TWO CENTS

TORONTO DOCTORS ON TRACK OF DIABETES CURE

RAILROAD UNIONS IN U.S. MAY JOIN IN MINERS' STRIKE

Coal-Diggers Expect Walkout to Be Hundred Per Cent. Effective.

PLANS ARE MATURING

President Harding May Make a Public Appeal for Conciliation.

DIABETES SUFFERERS GIVEN MESSAGE OF HOPE

Discovery Made at University of Toronto Will Be Means of Prolonging Life Considerably—F. G. Banting and C. H. Best Pushed Experiments All Last Summer.

BANTING STAKES HIS ALL ON THE RESULT

"DRY" LAWS HERE CAUSE HARDSHIP IN OLD FRANCE

French Government Anxious for New Trade Agreement With Canada.

HOME FOR STUDENTS

Opportunity for Our Lumbermen, Says Philippe Roy the Commissioner.

RESERVES OF COAL ARE HIGH IN CITY, PRICE TO GO DOWN

After Strike Trouble Prominent Dealer Looks for a Decline.

SHUT DOWN IN WEST

Canadian Diggers to Go On Strike With the United States Unions.

HAVE THEY ROBBED DIABETES OF ITS TERRORS?

CIVIL WAR STAGE NOT YET REACHED, BUT DANGER GREAT

People on Both Sides of Ulster Border Apprehend an Attack.

NERVES ALL ON EDGE

No Real Massing of Troops Yet, But Many Harrying Raids.

Imperials May Separate Irish

Figure 1. Front page report on the discovery of "an active pancreatic extract" by Banting (top left), Best (top right), Macleod (bottom left) and Collip (bottom right) published in the Toronto Daily Star on 22 March 1922. The text of the report can be read here: https://insulin.library.utoronto.ca/islandora/object/insulin%3AC10026. [Image Public Domain from Toronto Star archives]

Credible	Actual
Captain Frederick Banting, serving as a battalion medical officer in the First World War, is killed on 28 Sept 1918, hit by shrapnel from an exploding bomb.	Captain Frederick Banting, serving as a battalion medical officer, is wounded by shrapnel on 28 Sept 1918 but survives. He dies in a plane crash in 1941 on a secret military mission during the Second World War.
Professor Israel Kleiner demonstrates the ability of pancreatic extract to lower blood glucose in diabetic dogs, prompting a team of biochemists to purify the internal secretion in 1919. It is effective in treating diabetic patients.	Professor Israel Kleiner demonstrates the ability of pancreatic extract to lower blood glucose in diabetic dogs. A lack of support forces him to abandon his experiments.
Banting, an avid reader, devours all available literature on isolating the pancreatic internal secretion. He considers it an intractable problem and loses interest.	Banting, ignorant of the vast diabetes literature, reads Barron's article on the pancreas. It inspires him to approach Macleod, proposing his idea involving ligation and grafting of dog pancreas.
Best and Clarke Noble toss a coin to determine who will help Banting in the lab. Noble wins, but little progress is made due to personality clashes with Banting. On his return from Scotland in Sept 1921 Macleod is unimpressed and terminates the project.	Best wins the coin toss and forms a close and effective working relationship with Banting. Their progress is sufficiently impressive that Macleod extends and expands funding of the project.
Collip is recruited by Macleod but is unable to produce an extract of sufficient purity to treat patients. The project stalls, the Toronto group adding to the list of researchers who fail to progress to clinical tests of their extract on patients.	Collip successfully purifies the extract after only a few weeks work; his success leads to testing the extract on diabetic patients. Only later does Collip lose the knack of preparing the extract, his place taken by Best who continues with the purification.
The first diabetic patient, Leonard Thompson, treated with extract prepared by Banting and Best, dies as a result of hypoglycaemia. The programme is terminated.	Leonard Thompson is successfully treated with Collip's extract, the first evidence of the success of the extract in treating diabetic patients.
Insulin is discovered in the US. Eli Lilly is granted exclusive rights to manufacture insulin and becomes the dominant supplier of insulin globally.	Macleod invited Nobel laureate Professor August Krogh to visit Toronto. Krogh returns to his native Denmark and establishes Nordisk Insulin Laboratory, later Novo Nordisk, one of the three main global suppliers of insulin.

Table 1. Actual and alternative history of the discovery of insulin.

Macleod's support	Banting's reaction
Macleod offers Banting lab space to carry out experiments based on Banting's experience as a surgeon.	Banting kills 7 out of 10 dogs due to surgical incompetence with no scientific gain.
Macleod provides Banting with a lab assistant, Charlie Best.	Banting confronts Best whom he blames for unsuccessful experiments.
Macleod supplies Banting with upgraded lab facilities and provides him with a backdated stipend.	Banting complains Macleod is stealing his idea.
Macleod provides Banting with an expert in biochemistry, James Collip, to aid in the purification of the extract.	Banting confronts Collip, who refuses to tell him the method for successful extraction of insulin.
Banting and Macleod are announced as Nobel Prize winners.	Banting rushes to the laboratory intent on confronting Macleod.
Macleod takes Best and Banting to Yale to present their data to the world's leading diabetologists.	Banting's presentation is a fiasco and undermines the credibility of the experimental results. Macleod is forced to intervene and proprietarily reassures the audience of the validity of the data, a move that Banting interprets as stealing credit.
Macleod always credits Banting with initiating the research and contributing important experimental data.	Banting's supporters publicly denigrate Macleod and his contribution to the discovery of insulin.

Table 2. Banting's reaction to Macleod's support.

such as Einstein's theory of relativity or Darwin's theory of evolution by natural selection. The discoveries of insulin and the structure of DNA were areas of intensive research, and had Banting *et al*, and Professor James Watson and Professor Francis Crick failed in their endeavours, others would rapidly have succeeded, in the case of insulin within a few years and with DNA likely within a year.

Among the relatively recent medical discoveries including the smallpox vaccine, antibiotics, anaesthesia, oral contraceptives and chemotherapy, the discovery of insulin was the most accessible of the low-hanging fruit. It was based on a straightforward premise understandable by any competent researcher: the islets of Langerhans in the pancreas produce the internal secretion (insulin), which controls blood glucose levels. Given that hyperglycaemia resulting from insufficient pancreatic insulin production is the cardinal feature of diabetes mellitus, judicious preparation of pancreatic extracts would isolate insulin, which could be used to treat diabetic patients. The relative simplicity of the idea and the urgent need to develop effective therapies to treat diabetes attracted up to 400 research groups by 1920, who attempted isolation of insulin. They all failed. A confounding factor, accepted by many contemporary researchers, was that the external secretion degraded the insulin, accounting for its unpredictable potency, thus a means of isolating the insulin from the external secretion was required before the purification process could be applied to homogenised pancreas. This concept was wrong, as the external secretion was stored in the pancreas in an inactive form, but it led to delays in progress as researchers tried in vain to develop methods for removing the external extract.

"The relative simplicity of the idea and the urgent need to develop effective therapies to treat diabetes attracted up to 400 research groups by 1920, who attempted isolation of insulin."

Banting and Best's initial experiments showed promising results, but toward the end of 1921 they were unable to produce sufficient extract using the ligature procedure. More out of desperation than insight, they prepared extract from whole dog pancreas, then cow pancreas, both of which were successful in reducing blood glucose levels. Given the momentum of the research, Banting and Best never stopped to consider the profound implications of their results: the external secretion does not degrade the internal secretion, and Banting's idea to ligate the pancreatic ducts was wrong and could not lead to success. At the suggestion of Macleod they used alcohol as a solvent, and were soon joined by Collip who successfully isolated an extract of sufficient purity to test on diabetic patients. The treatment of diabetic patients with subcutaneous injection of insulin was not only a major advance in treatment of diabetes, but established an important clinical principle. Many other diseases also result from a deficiency in a naturally produced compound e.g. Parkinson's disease and Addison's disease result from deficiencies in production of dopamine and cortisol, respectively. As with diabetes, they can be treated by exogenous introduction of the deficient compound.

A bitter victory

This brief account glosses over the incompetence, failure, ignorance, conflict, misunderstanding, suspicion, fear and finally triumph that defined the project. The core conflict lay in Banting's belief that Macleod was taking undue credit and stealing his data. While it was true that Macleod did not carry out any of the experiments, he did fund, support and advise on the project and was justified in referring to "our" experiments when presenting the data at conferences.

This transformed Banting's already heightened feelings of simmering resentment into hatred and relations within the group were irrevocably damaged. The final insult to Banting's already fragile ego was Collip's rapid success in purifying the extract where he and

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Figure 2. The miracle of insulin therapy. Patient JL aged 3 years suffering from type 1 diabetes. Weighed 15 pounds on 15 December 1922 (left), but after undertaking insulin treatment was transformed, weighing 29 pounds by 15 February 1923 (right).

Best had failed. Controversy relating to Nobel Prize awards is common, but it is unusual that a nominee threatens to refuse the prize in protest to sharing the award with a colleague. Banting would rather sacrifice the most prestigious award in science than share it with the charlatan Macleod. Wiser counsels soon prevailed and for the sake of the reputation of the University of Toronto he accepted the award, sharing half of his prize with Best.

Many of Banting's colleagues in Toronto considered him a mediocre scientist; whatever his own research talents they were overshadowed by those of his two colleagues, Macleod and Collip. However, it is vital to realise, as Banting himself never could, that the success of the discovery of insulin lay in the collaborative effort of four individuals, a Scot, an American and two Canadians, each of whom contributed complementary skills to tackle the problem. Banting displayed astute judgement in approaching Macleod, the most suitably qualified researcher in Canada, with his proposal. Macleod recruited Best, whose personality meshed with Banting and they formed a supportive and effective partnership. The introduction of Collip to the group was an inspired idea, his expertise in biochemical techniques far superior to those of Banting and Best. Banting's claims for credit always reverted to his idea. That the idea was not original (at the start of the experiments Banting was unaware of the majority of the diabetes literature), or even correct, escaped Banting. What he did not appreciate was that his idea was the catalyst that allowed him access to a functional, well-funded laboratory, and most importantly the privilege of working with three equivalently passionate and committed researchers who laboured together towards a common goal.

A war hero's legacy

What is Banting's legacy? He is often described as a country boy who had difficulty adapting to cosmopolitan city life. He was also a decorated war hero who selflessly dedicated himself to helping his fellow soldier. Although naïve as a researcher he struck gold with his idea about diabetes, which precipitated the discovery of insulin. However, he was unable to rejoice in his discovery and the countless lives it saved, and later became frustrated with his inability to reproduce his success in the field of cancer research. He died in a plane crash on a secret military mission to England in 1941 as part of a study on aviation medicine.

I think of Frederick Banting in the following context. Images of diabetic patients in Toronto prior to the introduction of insulin still have the power to shock, as current patients receive treatment before they reach such a wretched and emaciated state. The resurrection of Teddy Ryder and Elizabeth Hughes, among the first diabetic patients successfully treated with insulin, is a testament to its life-saving effects. No patient in 1922, their families, or the embattled doctors treating them would argue that insulin therapy was anything other than a miracle.

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Nutritional supplements to reduce muscle damage and enhance athlete recovery

What is the physiological evidence?

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In the lead-up to the Olympics this summer, athletes will be looking for strategies to maximise their performance. One popular strategy is the use of dietary supplements. Many reasons for the use of dietary supplements have been reported in the scientific literature, including in the support of athlete recovery (Maughan *et al.*, 2018). Some of the most common supplements used by athletes are protein and creatine, but what about other nutrients? Can vitamin D boost recovery times? Can beetroot juice attenuate muscular soreness? In this article, we examine the benefits of vitamin D, tart cherry juice, and beetroot juice.

An important aspect of athlete recovery is exercise-induced muscle damage (EIMD), which can be triggered by various modes of exercise, including resistance training, prolonged running, and intermittent high intensity exercise (Owens *et al.*, 2019). Mechanistically, EIMD results in muscle structure damage, muscle soreness, decreased range of motion, and impaired force-producing capacity. EIMD is known to occur in two phases. The first phase involves initial structural damage resulting from mechanical and metabolic stress during exercise (Owens *et al.*, 2019); and the second phase involves inflammatory responses to damaged tissue. This occurs in the hours/days post-exercise, and is considered an important part of the muscle repair process (Harty *et al.*, 2019). The temporary loss of muscle functional capacity in the second phase and the increase in muscle soreness can be detrimental to athlete recovery and can impede next-day training sessions and/or performance. Therefore, nutritional interventions are frequently used to accelerate muscle recovery and ameliorate muscle soreness (Owens *et al.*, 2019).

Vitamin D

Vitamin D signals via vitamin D receptors (VDRs) to maintain optimal bone health, regulate muscle growth, and support immune function. Vitamin D comes in two forms: ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Vitamin D_2 is obtained through diet (e.g, animal sources, fortified foods); and vitamin D_3 is synthesised in the skin via a reaction triggered by sunlight, although vitamin D_3 can also be introduced through animal sources and fortified foods in the diet. Staggeringly, up to 62% of athletes (depending on the time of year and geographic location) could have blood vitamin D levels of < 50 nmol·L^{-1} (Maughan *et al.*, 2018). As this is considered suboptimal for most people, and considering the vital roles played by vitamin D, many governments recommend vitamin D supplementation particularly throughout the autumn and winter months.

Despite this recommendation, it is estimated that approximately only 7% of athletes use vitamin D as a performance supplement

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(Harty *et al.*, 2019). There is some evidence that a high daily intake of vitamin D (up to four times the recommended guidelines of 1000 IU·d^{-1}) may have a positive impact on athletic recovery. This is possibly due to the role of VDRs in activating the expression of genes that influence muscle growth, particularly in fast-twitch fibres. These effects on recovery, however, are likely dependent upon two factors: the type of vitamin D and baseline levels.

Vitamin D_3 supplementation has been shown to reduce circulating fatigue-related biomarkers (e.g. alanine and aspartate aminotransferases) after isokinetic force when compared with a placebo (Barker *et al.*, 2013). The effects of vitamin D_3 were both immediate (i.e. 1 hr post-exercise) and delayed (i.e. 24, 48, 72, and 168 hours post-exercise). However, these indicators of improvements in athletic recovery either decrease or disappear when vitamin D_2 is supplemented. This is likely because as vitamin D_2 levels increase with supplementation, it negatively impacts vitamin D_3 and therefore the total bioactive vitamin D levels. Vitamin D supplementation has been shown to benefit recovery when baseline concentrations are < 50 nmol·L^{-1} (Maughan *et al.*, 2018), with adequate concentrations in athletes considered to be > 50 nmol·L^{-1} . This is likely because of the role vitamin D plays in the regulation of calcium and phosphate transport, which directly affects muscle cell growth. It is worth noting, however, that this evidence is based on very few studies, hence the results are suggestive rather than conclusive.

Tart cherry juice

Tart cherry juice is rich in anthocyanins, a type of flavonoid pigment possessing antioxidant and anti-inflammatory properties. This is important because although an inflammatory response is needed for muscle repair and growth, prolonging the response can lead to EIMD including soreness and reduced muscle function (Owens *et al.*, 2019). The antioxidant and anti-inflammatory effects of tart cherry juice can dampen this inflammation and reduce EIMD, meaning athletes can compete and train more frequently (Harty *et al.*, 2019). The supplementation of tart cherry juice appears to effectively reduce the effects of EIMD and oxidative stress, and therefore allows athletes to recover, train, and compete more frequently. One study found that after 3 days of supplementation with 340 mL of tart cherry juice both in the morning and evening, EIMD-related symptoms (e.g. strength loss, pain) were significantly decreased in healthy college-aged male athletes, while force production increased by approximately 19% compared with placebo (Connolly *et al.*, 2006). Furthermore, short-term consumption of cherry skin powder for 7 days in resistance-trained male athletes reduced the perceived soreness by an average of 44% during the 48 hours after exercise (Levers *et al.*, 2015).

The study authors also reported increased recovery of serum total protein by 6%, which also aids in the muscle recovery process. Chronic consumption of tart cherry juice (i.e. approximately 60 mL of juice concentrate or 500-750 mL of juice or 480 g of cherry skin powder per day for 7-8 days) appears to ameliorate declines in muscle function (Brown *et al.*, 2019), reduce biomarkers of EIMD, and decrease perceptions of pain in both male and female athletes and non-athletes when compared with placebo controls (Harty *et al.*, 2019). Therefore, this strategy could have multiple benefits, particularly for those individuals who train frequently (both endurance and strength sports) and/or for those who have multiple events in a short period of time. It's been stated that the mechanism behind tart cherry's health benefits is due to the bioactive compounds, including various polyphenolic compounds that act as high level antioxidants (Harty *et al.*, 2019).

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"Although the promise of nutritional supplements may offer a beneficial strategy to support training recovery, and ultimately performance, our recommendations would be to focus on a wholefood-first approach."

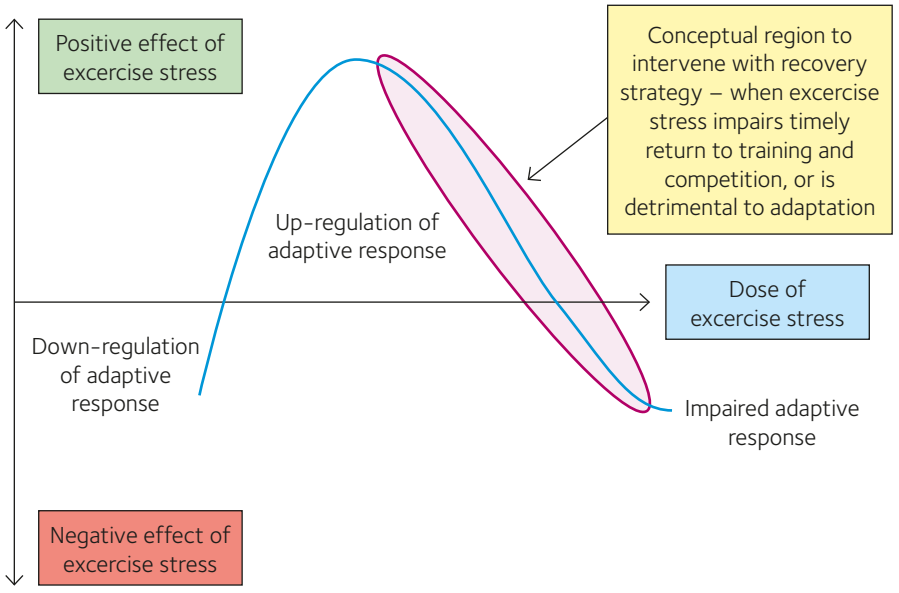

Figure 2. The hormesis model of recovery from exercise-induced muscle damage (EIMD), with implications to potential nutritional strategies [© 2018 European College of Sport Science. Taken from Owens *et al.*, 2019]

Beetroot juice

Beetroot juice may also reduce the effects of EIMD. This is possibly because of nitrates in beetroot and betalains, a type of pigment, again with antioxidant and anti-inflammatory properties similar to tart cherry juice with similar positive health effects and mechanisms (Clifford *et al.*, 2016). Additionally, following ingestion, nitrate is converted to nitrite in the blood (Jones, 2014). In conditions of low oxygen availability, nitrite can be converted into nitric oxide, which is known to play several important physiological roles. These include regulation of blood pressure, enhancement of muscle efficiency, lowering the oxygen cost of submaximal exercise, and enhancing exercise tolerance and performance (Clifford *et al.*, 2016).

The consumption of either high (1.75 L) or low (0.875 L) doses of beetroot juice was found to significantly increase recovery of repeated performance in countermovement jumps over 48 and 72 hours following exercise in recreationally active males (Clifford *et al.*, 2016). On average, the high-dose group maintained performance up to 91.7% at 48 hours post exercise and 93.4% 72 hours post excercise, corresponding to a 16.4% and 7.3% improvement in recovery when compared with isocaloric placebo. The low-dose group saw a similar improvement, which was not significantly different when compared with the high-dose group. Additionally, it has been demonstrated that beetroot concentrate improved running speed/pace over a 10 km course by 2% in both male and female competitive triathletes when administered at 100 mg·d^{-1} for 7 days (Montenegro *et al.*, 2017) whilst simultaneously improving muscle oxygenation and mitochondrial efficiency (Jones, 2014). These aided in recovery and performance, and reduced the degree of EMID outcomes, such as muscle soreness, reduced range of motion and impaired muscle force production.

If some is good then more must be better?

Some athletes and recreational exercisers assume that if a small dose of a supplement yields benefits then taking more must be even better. However, there is little evidence to support this assumption, and, for some supplements, increasing the dose can increase the risk of toxicity. Regarding vitamin D supplementation, for example, there is no evidence that supplementing more than 4000 IU·d^{-1} has any added benefits to athletic recovery (Owens *et al.*, 2019). Similarly, for both tart cherry and beetroot juice, a recommended dose of approximately 60 mL of concentrate (~500-800 mL of juice or 480 g of cherry skin powder) throughout the day for at least 3 days appears to be advantageous to an athlete's performance and recovery (Brown *et al.*, 2019). Although, juice doses of 1.75 L·d^{-1} have been shown to still have positive effects without any signs of toxicity, suggesting that a higher dose is possible (Harty *et al.*, 2019; Clifford *et al.*, 2016). It is worth noting that, although nitrate is not generally considered toxic, there is the possibility of toxicity with the use of nitrite salts owing to haemoglobin oxidation (Jones *et al.*, 2014). As such, it is recommended that athletes use natural

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vegetable products and trial their use prior to competition to optimise supplementation strategies and avoid any potential negative effects.

Discount the placebo effect at your peril!

This article has discussed the potential benefits of novel supplements to improve athletic recovery. And yet, there is one effect that has received more attention than all of the others put together: the placebo. There is extensive evidence that placebos are effective, with people who take them exhibiting significant improvements in athletic performance and in post-exercise recovery (Clifford *et al.*, 2016; Brown *et al.*, 2019). Thus, it would seem that if an athlete believes that a supplement will help in athletic recovery, it is likely that the placebo effect will make it so. Nevertheless, studies have shown that nutritional supplements, including vitamin D, tart cherry juice, and beetroot juice can improve the recovery of muscle function by alleviating markers of EIMD compared with a placebo (Harty *et al.*, 2019). Scientific research undoubtedly presents evidence of the effects of nutritional supplementation providing a genuine physiological effect, which reduces EIMD and enhances performance and recovery. However, the power of the placebo effect also unquestionably affects these outcomes.

Other nutritional supplements

We should acknowledge that although vitamin D, tart cherry and beetroot juice have been discussed in this article, there are other nutritional supplements and food items that have been demonstrated to reduce EIMD and enhance the recovery of athletes. These include creatine monohydrate, omega-3 fatty acids, protein (i.e. whey), watermelon juice, and pomegranate juice (Harty *et al.*, 2019). Additionally, there are a plethora of other nutrients and/or food items that mechanistically could offer therapeutic potential, and further research is clearly warranted in this domain; for example, bromelain (found in pineapple), ginger, curcumin, ß-hydroxy-ß-methylbutyrate (HMB), quercetin, cocoa, and caffeine. However, it should be highlighted that a natural, wholefood-first approach in athletes should be endorsed as a primary starting point. Nutritional supplements should only be used to complement a phytonutrient, protein-rich diet to support exercise recovery where scientific evidence, consideration of product safety, and pertinent application exist.

Practical applications

Strategies in combatting EIMD via nutrient supplementation must consider the chronic application of many of these as they may impair long-term adaptations (Harty *et al.*, 2019) given that oxidative stress and inflammation play an important role in many skeletal muscle adaptations including growth, strength and hypertrophy (Owens *et al.*, 2019). However, maximising recovery capacities at the cost of long-term training adaptations may be advantageous in athletes who need to recover quickly between training sessions and events. It is also noteworthy that the chronic and persistent use of nutritional supplements to alleviate EIMD by attenuating the inflammatory response may subsequently impair long-term muscle adaptations. Therefore, a periodised approach to supplementation may yield the greatest benefits to the athlete along with considering the trade-off between muscle recovery and adaptation (Owens *et al.*, 2019). Considering this, it is recommended that athletes work with a nutrition/medical professional and trial strategies before beginning any intervention, particularly for elite athletes and during competitions.

Although the promise of nutritional supplements may offer a beneficial strategy to support training recovery, and ultimately performance, our recommendations would be to focus on a wholefood-first approach (e.g. appropriate energy intake, sufficient protein quantity/quality, and a phytonutrient/polyphenol-rich diet) before considering supplementation. Additionally, with supplementation, the use of approved Informed Sport products should be considered to minimise risks of falsely advertised batch products. Finally, it may also be advantageous to implement practical treatment recovery (e.g. sports massage, ice bathing, stretching, foam-rolling etc) that can be used alongside nutritional strategies to maximise recovery and reduce the effects of EIMD. However, it's important to note that the research into applications of these supplementation are still in its infancy and longer-term studies are warranted.

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Avoiding the traveller's blues

Understanding the physiology of jet lag

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After the potential easing of lockdown restrictions was announced by the UK government in late February/early March, there was a flurry of holiday bookings to destinations abroad (BBC, 2021). If you are one of those with plans in place to go hopping over a few lines of longitude later this year (with destinations from Turkey to Mexico mentioned in reports), good timing will be necessary to avoid the traveller's blues. We do not mean good timing insofar as avoiding the disappointment of cancellation due to travel restrictions and public health priorities (although, of course, we hope this will not be the case for you). Rather, we mean from a biological time-keeping perspective to avoid the traveller's blues known as jet lag.

We all know what jet lag is...right?

Asking around might get you the answer, "*it is when you have difficulty sleeping because your body has not adjusted to the new time zone*". This doesn't sound too bad. There are nights when we do not sleep well but manage okay the next day. You might try the online blogs to get a sense of what is known by the wisened travellers. These descriptions of jet lag can be more colourful: "*drowsy at that late-afternoon meeting ... and every fibre of your being screams out 'go to sleep' ... trying to avoid the gerbil wheel of anxiety that kicks in when you're awake in the middle of the night*" (Williams, 2017). This sounds a bit worse. The medically orientated websites get a bit closer. The first few sentences on the NHS website are: "*Jet lag is when your normal sleep pattern is disturbed after a long flight. It usually improves within a few days as your body adjusts to the new time zone*" (NHS, 2020). Scrolling to the bottom of the page we can find: "*Jet lag can also sometimes cause dizziness, indigestion, nausea, constipation, changes in appetite and mild anxiety.*"

This is getting closer to the truth as it includes a few more symptoms of jet lag but still not quite there.

A flight from the UK to South Africa will take 11-12 hours – without question a long flight – but you won't experience jet lag. Fatigue and dehydration and their knock-on effects – caused by stress, high altitude, and long-haul – will be experienced, sure. But this is not jet lag in the conventional sense. The time difference between the UK and South Africa is 2 hours, meaning you might be having brunch instead of breakfast in South Africa. In contrast, the time difference between the UK and Mexico is 6 hours even though flight duration is approximately the same as UK to South Africa, meaning you may be getting hungry for breakfast at 2am in Mexico. Even the 6-hour time difference does not sound so bad if this were the only symptom. We could survive being hungry for a few hours until breakfast (just about) or could stay awake a few hours extra when needed (this will not be lost on lab bench physiologists) on the first evening at a new destination.

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World map of current official time zones. [Image from public domain by CIA.gov]

The trouble arises when the body attempts to adjust to the new time zone, which really becomes conspicuous from 24 to 48 hours after arrival, and can get worse before it gets better. The crook of the matter lies in circadian biology.

Circadian biology

Physiology comes with an innate circadian timing system (CTS). An expression loop of core clock genes with a period of ~24 hours (*circa dian* = approximately a day) gives rise to rhythmic expression of proteins, cell processes, and signalling, scaling up to rhythms in tissues, organs, and integrated physiology. These core clock genes are present in every cell; thus, we have a clock in every cell. When the clocks are synchronised, circadian rhythm in various integrated physiological processes can be observed. For instance, peaks in cognitive and physical performance can be reached that would otherwise be unreachable if clocks were not in synch. Coordinating the clocks is a central pacemaker situated in the suprachiasmatic nuclei (SCN) in the hypothalamus region of the brain. Neuroendocrine output from the SCN is the coordinating link to the rest of our cellular clocks. Peripheral clock feedback to the SCN is not as well understood.

Peaks in cognitive and physical performance would be no good to us if they occurred in the middle of the night rather than in the middle of the day, so the central pacemaker responds to the light and dark conditions of our environment to synchronise with the daily light–dark cycle. Retinal ganglion cells in the eyes, which express the light-sensitive protein melanopsin, note the prevailing light conditions and send a signal down the retino-hypothalamic tract to the SCN. The SCN output depends on the relative signal strength and timing (relative=relative to light history) of light. For instance, experiencing light a bit later in the evening than would be expected typically serves to phase delay circadian rhythms. As examples, the secretion of melatonin, which begins shortly before sleep, is delayed when evening light is prolonged and the night-time drop in core body temperature will also be delayed. This forms part of the rationale for not using bright, light-emitting devices at night as they can affect our circadian rhythms. We all present with phase response curves to light, insofar as the timing of the signal will have different strengths of delaying or advancing of rhythms (Fig. 1).

Clocking the traveller's blues

So, you arrive in the new destination, some lines of longitude away from home. For example, let us take a 12-hour difference in clock time and you arrive at either 3pm or 3am. The jet lag process will already have begun in terms of mild phase delay or phase advance due to the change in the timing of light and dark and your phase response curve. It is typically understood that we can only phase-shift by approximately 1 hour per day, but digging a bit deeper has shown that individual rhythms shift at different speeds. Remember, we need to phase-shift clocks in all cells throughout our body and the subsequent rhythms that they give rise to. After ~12 to 24 hours, a shift of 1 hour might not be noticeable and peaks and troughs in rhythms will still be observed; albeit perhaps a bit earlier or later than usual and maybe a bit smaller in amplitude due to a small misalignment among the individual clocks of your body. You will still be prone to being awake at night and sleepy during the day at your destination; however, you could sleep well during the daytime should you choose to do so as your rhythms that contribute to restorative sleep are only mildly misaligned with respect to each other after this short period at the new destination. The same holds for reaching high performance levels, just these would occur at night at your destination. Our CTS can manage this quite well; indeed, elite athletes take advantage of this to align the peak in performance rhythm with event time at their destination (Mascaro & Facer-Childs, 2020).

In the following days, however, as your individual clocks continue to shift toward being more in line with the environmental time, they will initially become more misaligned due to this shifting at different speeds (Fig. 2). Some integrated rhythms may even become non-existent due to a lack of overlapping peaks and troughs in various cellular rhythms. This more severe misalignment gives rise to the poor sleep quality (regardless of sleep timing), dizziness, indigestion and nausea, constipation, changes in appetite, and anxiety symptoms as described by the NHS website. Other symptoms, already noted as potentially important in the 1960s and 70s include perturbation of mood and decision-making abilities (noted for its importance to travelling business persons and diplomats) (Rockwell, 1975). You might take this into account when socialising with colleagues late into the evening or asking pertinent questions at the next annual Physiology conference after trans-meridian travel.

These periods of disarray are what correspond to *every fibre of one's being screaming for sleep* and determines the real traveller's blues. Some people will suffer more or less than others due to experience with jet lag, age, stress levels, genetics, the direction of travel, and other factors that may affect how sensitive the CTS is to phase-shifting.

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"Trouble arises when the body attempts to adjust to the new time zone, which really becomes conspicuous from 24 to 48 hours after arrival, and can get worse before it gets better."

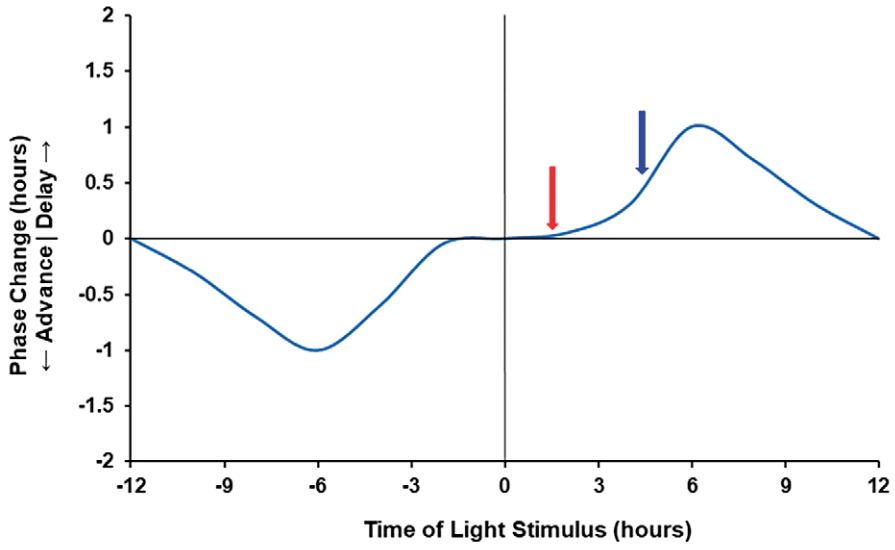

Figure 1. **Hypothetical phase response curve.** The magnitude of phase change is plotted as function of the timing of light stimulus. Note the curve is not a circadian rhythm *per se,* rather it is how a rhythm would respond depending on the timing of light stimulus. The time of light stimulus (x-axis) is arbitrarily labelled. In this hypothetical example, time 0 corresponds to the mid-point of one of the dead zones, i.e., when no phase change will occur in response to the stimulus. The other dead zone occurs at time of light stimulus ~+12/-12 hours from time 0. Light exposure at ~1.5 hours post time 0 (red arrow) has little to no effect on delaying the circadian phase of the measured rhythm. Light exposure at ~4.5 hours post time 0 (blue arrow) has a much more conspicuous effect. An example rhythm particularly susceptible to light is that of the hormone melatonin. In the typical case of melatonin, time 0 would be the middle of the daily light period. Post time 0, getting closer to the daily dark period, light stimulus has increasing strength to delay the melatonin rhythm. With transmeridian travel across 6 time zones, time 0 for the melatonin response would be shifted by 6 hours; thus, no longer in the middle of the daily light period at the new location.

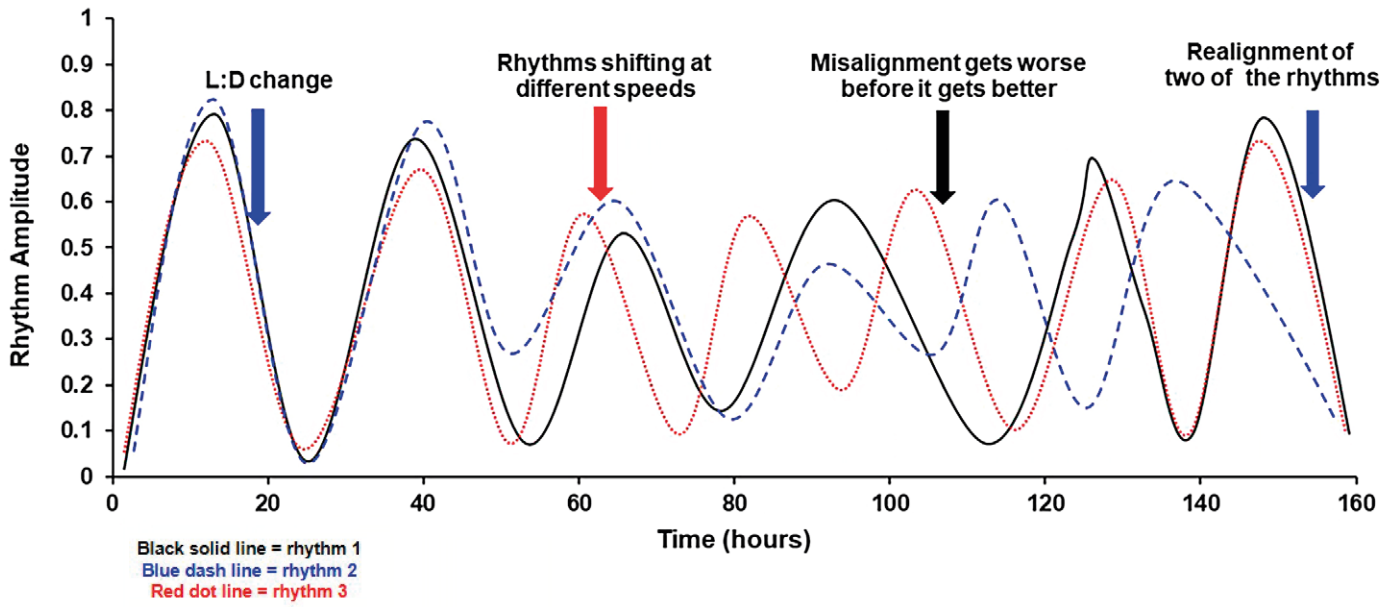

Figure 2. **Hypothetical example of circadian rhythms phase-shifting to a new light–dark cycle.** The first blue arrow indicates the time of change in the light–dark (LD) cycle, as occurs when flying to a new time zone (for simplicity, this can be the time of arrival; of course, a new time zone can already be experienced while in transit). The rhythm indicated by the solid black line is delayed more than the red dotted line and blue dashed line at the red arrow; i.e. the three rhythms are shifting at different speeds. Rhythm amplitudes, in this hypothetical example, are also diminished. After another ~2 cycles, there is greater misalignment. After another ~2 cycles, the peak amplitudes for the two rhythms are again reached. After a few more cycles, the blue rhythm will eventually realign with the red and black rhythms.

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As days pass, cellular rhythms gradually come back into alignment and symptoms will disappear. The CTS will then be entrained to the prevailing conditions of the new environment (Fig. 2). In the case of a 12-hour time change, with the assumption that rhythms can shift by approximately 1 hour per day, it would take 12 days to become fully realigned, although some rhythms may align with the prevailing environmental time faster than others.

Prevention or cure?

Neither, unfortunately, or at least not completely if flying is a necessity (though we would encourage more eco-friendly travel and avoiding travel by plane). Melatonin is touted as a candidate pharmacological aid, but it must be timed correctly (in accordance with phase response curves to melatonin; similar to light in Fig. 1). Ultimately, it will not facilitate immediate adaptation to more extreme destination time zones. Melatonin does have, *inter alia*, sleep-promoting properties as it "opens the sleep gate" but this does not necessarily mean it will affect circadian rhythm. The purported benefits may stem simply from feeling more refreshed after sleeping. To exemplify some complexity, if you are flying into a destination at night time that would otherwise still be your day time (i.e. as might occur if you fly east – the sun rises in the east and sets in the west; thus, you and the setting sun approach each other), then taking melatonin may be useful to advance sleep. Your sleeping can also affect your light–dark exposure while travelling; thus, being asleep also means not experiencing light while travelling that would otherwise serve to delay sleep.

Asking "Google" for help may not always be ideal. An online newspaper article in 2019 claimed a pilot indicated a few glasses of red wine prevented his jet lag. This is definitely not recommended as alcohol decreases sleep quality. If you land on the NHS website, you will find good advice such as to avoid sleep and seek daylight during the daytime and use an alarm to prevent oversleeping in the morning. Regarding the latter, more gradual phase advance or delay of sleeping patterns might be preferred, if possible, to prevent rhythms trying to shift too far too fast (remember, different rhythms shift at different speeds and bigger shifts will mean more misalignment). Caffeine may be useful to increase alertness but will not speed up adaptation, rather it plasters over the temporarily decreased alertness. Also, it is unlikely to cover up other adverse effects of misalignment. But, be careful, as caffeine could make you feel worse once it wears off, and should not be viewed as a substitute for water, with dehydration being a consequence of air travel. Other tips to help with sleep include a hot bath or shower in the evening to hasten the change in core:skin temperature ratio that is associated with sleep.

There is a Physiological Society video on YouTube that suggests timed vasopressin in eye drops could become a remedy or "cure" (The Physiological Society, 2018). We remain sceptical as this is designed toward only affecting the CTS and not peripheral clocks.

Circadian rhythm phase-shifting can be kicked off prior to travelling and this is probably the best bet to beat jet lag by either delaying or advancing circadian rhythms in smaller increments (perhaps 30 mins per day). Seeking light just before bed and seeking more darkness in the morning will start the process of delaying sleep if you are travelling west. The opposite light exposures should be used for travelling east. Food timing and activity timing may also be shifted accordingly to provide benefit (Lewis *et al.*, 2018, 2020). A little bit of chocolate for breakfast has been shown to aid entrainment to new light–dark cycles in rodents (Escobar *et al.*, 2020) – something many could get on board with – although this may have something more to do with specific nutrient content than chocolate *per se*. Research into non-light circadian time cues is ongoing. Overall, pre-travel phase-shifting in smaller increments can prevent larger cognitive and physical deficits in performance and other jet lag symptoms.

Conclusion

So, to avoid the traveller's blues if you find yourself crossing meridian lines this summer, Rockwell's timeless letter, which already pointed to "*both external desynchronosis (inside time versus outside time) and internal desynchronosis (with ≥ two rhythms being out of synchronosis with each other) associated with temporal translocations of three hours or more"* and provides advice (from an American vantage) is still... well, timeless (Rockwell, 1975):

- For short stays it is best to stay on "home" time;
- When travelling west to east go to bed progressively earlier before the trip (vice versa east to west);
- For important meetings leave several days earlier (our findings indicate that 48 hours are needed for resynchronosis);
- Arrange important activities at your normal peak times – meet your European colleagues in late afternoon or evening;
- Use food and alcohol sparingly during the flight and the first three days after arrival – alcohol (and most tranquilisers and hypnotics) interferes with rapid eye movement (REM) sleep;
- On long transmeridian flights arrange a halfway stopover;
- Arrange your schedule to shorten the day rather than the night;
- Rest and relax for two days before working.

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An introduction to Stewart acid–base

Clinically useful or chemical bookkeeping?

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Puissance de l'hydrogène or "power of hydrogen" is what I was taught to be the origin of pH; this is likely incorrect (Kenny and Goldfarb, 2012). In the early 20th century Sørensen, a Danish chemist studying beer-producing enzymatic reactions, quantified hydrogen ion concentration [H^+] with the pH scale. Yet the derivation of pH in Sørensen's manuscript arose from solving an equation with two unknowns (labeled p and q) such that the p in pH reflected mathematical notation rather than *puissance*. The power of protons [H^+] in biological reactions cannot be over-emphasised. Waxing and waning [H^+] alters enzymatic and cellular activity amongst other biological consequences. With acute effects on cardiovascular, respiratory and neurological function, severe pH changes are life-threatening, therefore, understanding acid–base disturbances in human health is critical.

The primary purpose of this brief review is to introduce the reader to an acid–base paradigm codified and quantified by the Canadian physical chemist Professor Peter Stewart. There are many excellent reviews for more in-depth reading (Rastegar, 2009; Kurtz *et al.,* 2008; Story, 2004; Sirker *et al.,* 2002). Stewart's approach is gaining traction in clinical medicine – primarily amongst intensivists and anaesthesiologists. It is particularly useful when thinking about metabolic pH disturbances because it adopts a broader definition of acids and bases. Arguably, the Stewart approach better explains pH variation associated with albumin and chloride concentration changes. However, others posit that mechanistic cause-and-effect is lacking and Stewart's formulation is merely chemical book-keeping. While this debate is likely to continue, the student of health sciences is likely to encounter the Stewart approach, so a basic understanding is warranted. Prior to outlining the fundamentals of Stewart's concept, a cursory history of clinical acid–base is presented for context.

The traditional view of acid–base balance

At the turn of the 20th century, the definition of an acid, as championed by Naunyn, was somewhat of a conglomeration (Story, 2004). It included the description of an acid as something that, in water, elaborated protons – as per Arrhenius. But an acid also encompassed anions (e.g. chloride) based on what Faraday had previously conceived. Per this approach, electrolytes such as sodium and chloride are considered base and acid, respectively. Indeed, there is a direct line between Naunyn's formulation to Van Slyke in 1920 and then Singer and Hastings in 1948 who coined the term "buffer base" (BB). BB is calculated as the difference between all of the completely dissociated cations (i.e. total base) and anions (i.e. total fixed acid) – a difference

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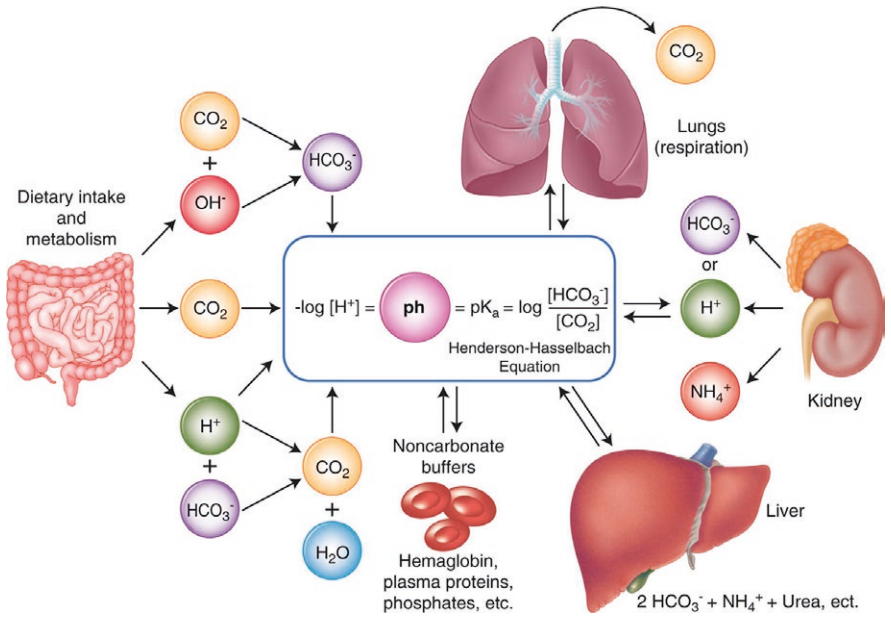

Figure 1. Organ system contributions to acid–base balance under the traditional Henderson–Hasselbach model. [© 2020 Springer Nature Switzerland AG 2020. Reed *et al.,* 2020. http://doi.org/10.1007/978-3-030-39781-4_3]

"The primary purpose of this brief review is to introduce the reader to an acid-base paradigm codified and quantified by the Canadian physical chemist Peter Stewart."

filled by *buffer base*, that is, bicarbonate and weak acid anions (e.g. albumin and phosphate). Of note, this general acid–base model (encompassing cations and anions) was the predominant clinical concept until the mid-20th century when it was supplanted by what is currently termed the "traditional" approach, described below.

However, at variance with the description above, another impression of clinical acid–base took shape – one with which most clinicians are familiar today. In 1909, Henderson combined equilibrium constants for the relationships between carbon dioxide [CO_2], water, carbonic acid, bicarbonate [HCO_3^-] and [H^+]. With this, Henderson advanced direct and indirect quantitative relationships between [H^+], dissolved [CO_2] and [HCO_3^-], respectively. Shortly thereafter, Hasselbalch incorporated Sørensen's pH scale to derive the oft-taught Henderson–Hasselbalch equation (Fig. 1) (Kurtz *et al.,* 2008; Sirker *et al.,* 2002):

(1)
$$pH = pK + \log \frac{[HCO_3^-]}{S_{CO_2} x\ P_aCO_2}$$

Here, pK is the acid dissociation constant (6.1), S_{CO2} is the solubility coefficient for CO_2 (0.0307) and P_aCO_2 is the partial pressure of carbon dioxide in arterial blood. With this equation, the relationships between P_aCO_2, [HCO_3^-] and blood pH were made objective. In addition, the calculation enabled the sense that respiratory and renal physiology modulated pH via ventilation (i.e. carbon dioxide tension) and bicarbonate balance, respectively. This "bicarbonate-centered" formulation also comported with the contemporary Bronsted–Lowry definition of an acid – a substance capable of proton donation.

Thus, by the mid 20th century, clinical acid–base physiology was motored by the Henderson–Hasselbalch equation and propelled "trans-Atlantic debates" as to how pH disturbances are best judged (Rastegar, 2009). In Denmark, during the polio epidemic, Bjørn Ibsen realised that patients were dying not of alkalosis, as initially thought, but rather P_aCO_2 retention – which led to bicarbonate elevation. This insight was followed by the base excess (BE) calculation, proposed by Professor Siggaard-Andersen. BE is the amount of [H^+] titration needed to return *in vitro* blood pH to 7.4 at a P_aCO_2 of 40 mmHg. Across the Atlantic, however, Professor William Schwartz and Professor Arnold Relman argued that *in vitro* BE is problematic because it ignores whole body kinetics (e.g. the role of interstitial buffering) and chronic, renal compensatory responses (Schwartz and Relman, 1963). Thus, they proposed "rules of thumb" to help guide the clinician (e.g. for every 10 mmHg P_aCO_2 elevation, bicarbonate increases by 1 mEq/L acutely). Despite their different interpretations, both the "Copenhagen" and "Boston" schools of thinking were grounded by the Henderson–Hasselbalch perspective.

What distinguishes Stewart acid-base from the traditional approach?

A key criticism of the traditional, bicarbonate-centred approach is that it is merely a mathematical description of pH and fails to provide any mechanistic insight into rising and falling [H^+]. For example, the isohydric principle predicts that the [H^+] (and therefore pH) may be expressed by the ratio of *any* weak acid–conjugate base pair in a biological solution. Thus, blood pH could be equally well described by the ratio of HPO_4^{2-} to $H_2PO_4^-$; in other words, in terms of pH there is nothing unique about bicarbonate (Story, 2004). Consequently, the Henderson–Hasselbalch equation may lead clinicians into a "*computo; ergo, est*" fallacy (I calculate it; therefore, it is) (Wooten, 2004).

In response to these perceived shortcomings, Peter Stewart proposed a quantitative acid–base analysis in the late 1970s that is argued to provide true cause-and-effect relationships between *independent* and *dependent* variables, respectively (Stewart, 1978). In his formulation, there are 3 *independent* variables that clinically mediate both [H^+] and [HCO_3^-]:

1. P_aCO_2
2. The total weak acid concentration [A_{TOT}] (e.g. albumin, phosphate)
3. The strong ion difference [SID]

Accounting for the law of mass conservation, electroneutrality and equilibrium constants for all incompletely dissociated species in biological solution, Stewart derived a fourth-order polynomial equation expressing [H^+] as directly related to P_aCO_2 and A_{TOT} and inversely to SID (Sirker *et al.,* 2002).

SID is the difference between strong cations and strong anions in solution. "Strong" denotes how completely a species dissociates in a particular solution. In blood, the predominant strong ions are sodium [Na^+] and chloride [Cl^-] with small contributions from potassium [K^+],

magnesium [Mg^{2+}] and calcium [Ca^{2+}] (see Table 1). As SID may be simplified to [Na^+] less [Cl^-], its value is approximately +40 mEq/L in humans. For example, looking at a metabolic panel, you might see a [Na^+] of 140 mEq/L and [Cl^-] of 100 mEq/L. To think of how SID changes pH, keep in mind the imposition of electroneutrality in Stewart's system of equations. If P_aCO_2 and A_{TOT} were kept constant, but the SID diminished from +40 mEq/L to +25 mEq/L (e.g. hyperchloraemia from normal saline resuscitation), then the concentration of negatively charged, *dependent* species like bicarbonate would fall and positively charged, *dependent* species like protons would rise by mass action; thus, pH decreases.

The key to Stewart's paradigm is that both [H^+] and [HCO_3^-] are completely at the mercy of the three independent variables noted above. P_aCO_2, A_{TOT} and SID *independently* define the boundaries within which [H^+] and [HCO_3^-] *dependently* settle in the system. When sodium bicarbonate is administered intravenously, [H^+] falls not because of the addition of the dependent [HCO_3^-]; addition of the strong cation sodium raises the SID, which is the independent variable. On the other hand, intravenous hydrochloric acid (HCl) elevates [H^+] not because of the dependent proton within HCl; the strong anion chloride shrinks the SID, which is directly responsible for diminished pH.

How does the Stewart acid–base formalism change how we think about metabolic disturbances?

Considering the traditional, bicarbonate-centred approach and Stewart's model, one sees that P_aCO_2 is an independent mediator of pH for both. Therefore, in arterial blood, respiratory disturbances may be thought of similarly in either formulation. As a consequence, the crucial distinction between the two models is the treatment of metabolic disorders. In fact, a "corrected" Henderson–Hasselbalch equation has been proposed to include the true independent acid–base variables as follows (Kurtz *et al.*, 2008):

$$pH = pK + \log\frac{([SID] - [A^-])}{S_{CO_2} x\ P_aCO_2} \quad (2)$$

While the effect of P_aCO_2 is the same as the traditional model, falling SID (e.g. hyperchloraemia) or rising A_{TOT} (A^- is the conjugate anion of A_{TOT}) diminishes pH (i.e. increases [H^+]). Conversely, rising SID (e.g. hypochloraemia) and falling A_{TOT} both elevate pH.

While an in-depth description of metabolic alkalosis (Goldfarb and Kenny, 2019) is far beyond the intent of this brief primer, from Equation 2 above we see that increased SID and/or decreased A_{TOT} raise pH per the Stewart approach. The most common clinical causes of metabolic alkalosis are vomiting and diuresis. Both of these scenarios are marked by chloride loss, via the upper GI tract and kidneys, respectively; these processes raise the SID. Additionally, Stewart's model invites the clinician to consider loss of A_{TOT} as a mechanism of alkalosis, for example severe hypoalbuminaemia in critically ill patients (Story, 2004).

With respect to metabolic acidosis, confusion may arise given the important distinction between the "anion gap" (AG) and "strong ion gap" (SIG) in the traditional and Stewart approaches, respectively. Both gaps, ultimately, alert the clinician to the footprint of unaccounted anions in the blood; clandestine anions narrow the differential diagnosis of a metabolic acidosis. While both gaps are predicated upon electroneutrality, the fundamental difference between the AG and SIG is how anions are grouped during book-keeping (Fig. 2).

Measure	Median value	95% confidence interval
Sodium [Na+] mmol/L	138	138–139
Potassium [K+] mmol/L	4.0	3.9–4.0
Magnesium [Mg^{2+}] mmol/L	0.98	0.85–1.1
Chloride Cl [Cl^-] mmol/L	105	105–105
Bicarbonate [HCO_3^-] mmol/L	24	23.6–24.3
Ionized calcium [Ca^{2+}] mmol/L	1.21	1.20–1.22
Phosphate [PO_4^{3-}] mmol/L	1.29	1.12–1.45
Albumin g/dL	4.0	3.4–5.4
P_aCO_2 mmHg	38.3	37.5–39
Anion gap	11	9–13
SID_a *	41	
SID_e *	39	
SIG *	2	

* *calculated from equations (3), (4), (5)*

Table 1. Typical ranges of concentrations of major and minor plasma cations and anions, and calculated values.

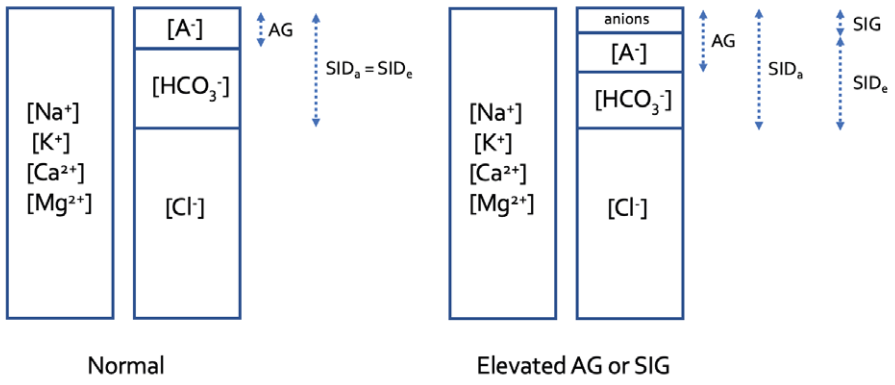

Figure 2. Graphical representation of cation (left columns) and anion (right columns) groupings according to anion gap (AG), strong ion gap (SIG), apparent (SID_a) and effective (SID_e) strong ion difference. [A^-] is the conjugate anion of the total weak acid concentration [A_{TOT}] (e.g., albumin, phosphate)

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The AG considers the difference between positive and negative charges only – agnostic to how fully dissociated or not the charged species is. The normal AG is almost entirely occupied by the negatively-charged albumin and, therefore, should always be corrected for by the patient's albumin concentration. As such, an AG of 12 could be quite elevated in a patient with very low albumin.

The SIG, however, partitions charged species into "strong" (e.g. sodium, potassium, chloride) and "weak" (e.g. albumin, bicarbonate, phosphate); the net balance between these two groupings should be zero when there are no hidden anions. These ionic factions are referred to as apparent SID (i.e. SID_a) and effective SID (i.e. SID_e), respectively (Fig. 2) (Rastegar, 2009). In the calculation of SID_e below, the three terms account for the concentration of bicarbonate, albumin and phosphate. Note that with this approach, albumin "correction" is built into the calculation, as opposed to the traditional, AG method. Also note how closely SID_e relates to *buffer base*, described above. Elevation of either AG or SIG should prompt a search for ketones, uraemia, lactate or toxic alcohols.

to declare the "end of the bicarbonate era" (Cove and Kellum, 2020). While debate is likely to continue, when used correctly, both models lead to similar clinical predictions (Rastegar, 2009).

Conclusion

As Stephen King noted, "sooner or later, everything old is new again." Peter Stewart's description of clinical acid–base in the late 1970s resonates with both *buffer base* and Naunyn's thinking in the early 1900s. Consequently, in the 1950s the Henderson–Hasselbalch approach was considered "modern" with respect to the older notion including anions and cations as mediators of pH. These schools have reversed over the last 40 years after Stewart provided a quantifiable framework based upon conservation of mass, electroneutrality and mass action that holds "strong ions" as independent determinants of $[H^+]$. While Stewart's theoretical approach is embraced as mechanistic, others argue that like Henderson–Hasselbalch, Stewart's equations do not offer cause-and-effect and are equally descriptive.

(3) $$SID_a = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-])$$

(4) $$SID_e = [HCO_3^-] + [A^-] = 12.2\ x\ \frac{P_aCO_2}{10^{-pH}} + \left[albumin\ in\ \frac{g}{L}\right] x\ (0.123\ x\ pH - 0.631) + \left[PO_4^-\ in\ \frac{mmol}{L}\right]\ x\ (0.309\ x\ pH - 0.469)$$

(5) $$SIG = SID_a - SID_e$$

Association or causation?

While the proponents of Stewart formalism argue that his equations are mechanistic rather than descriptive, critics maintain that Stewart's approach suffers from the same *computo; ergo, est* fallacy levied against traditionalists. Macroscopic electroneutrality, Stewart's critics argue, is a good way to tally charged species, but it does not necessarily speak to any underlying cause-and-effect process (Kurtz *et al.*, 2008). Further, electroneutrality may be violated. Consider oxidative phosphorylation, where the inner mitochondrial membrane is acidified without any clear change in SID or A_{TOT} (Kurtz *et al.*, 2008). How does the Stewart paradigm account for this ubiquitous physiochemical event?

On the other hand, a recent electrodialysis study established that both respiratory and metabolic acidosis could be corrected by selectively removing chloride (Zanella *et al.*, 2020)! Per the Stewart model, this is explained by rising SID – leading editorialists

Whether the student chooses to follow the traditional or Stewart approach to clinical acid–base, the following general guidelines are worthwhile:

1. Look at the pH first
2. Search for cryptic anions, even if there is primary alkalaemia
3. Remember albumin
4. Keep an open mind
5. Treat the patient, not the numbers

Disclosures

Dr Kenny is the cofounder and Chief Medical Officer of Flosonics Medical. He is the creator and author of a free haemodynamic curriculum at heart-lung.org.

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Air pollution and me

What do we know and what should I do?

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With the current results of an inquest into the role of air pollution in a child's death from asthma, air pollution and its health effects once again return to the forefront of mainstream media. The media brings the research to life with snippets of studies demonstrating effects from not only cars and industries, but also our home cooking habits. With the levels in the UK exceeding WHO guidance year on year, the focus now moves to what we can do about it. In order to answer this, we need to answer the question, what does air pollution actually do to our bodies and therefore what approaches are best taken to address the current crisis? In this article we will cover the health impacts of air pollution and how they may occur and touch upon ways to combat pollution exposure.

What is air pollution?

Air pollution is the presence in the air of a substance that has harmful or poisonous effects on living beings. Its sources vary depending on where you are in the country or the world, but they fall into two main categories: indoor and outdoor. Outdoor pollutants are primarily:

- Particulate matter (PM) – soot, smog, dust, with a carbon centre. These can be natural (such as sand from the Saharan desert), but typically come from combustion sources such as traffic-related air pollution (TRAP) from cars and lorries, and industrial processes.
- Nitrogen oxides (NOx)– gases generated by vehicles through combustion processes in the air. These gases are highly interactive with PM and often sit on their surfaces. The health impacts of exposure are closely linked to (and at times indistinguishable from) PM.
- Ozone (O_3) – formed when other pollutants (such as NOx) react in sunlight.

Indoor air pollution is becoming increasingly important in the UK and includes second-hand cigarette smoke, carbon monoxide (CO) and carbon dioxide (CO_2) from open fires and gas hobs, biological allergens (house dust mites and moulds) and our roast dinners and toast (specifically the fine particles released through the process of cooking and using gas hobs).

Particulate matter (PM) constituents depend heavily on the area, season and weather and are classified by size i.e. $PM_{2.5}$ (<2.5 microns) and PM_{10} (<10 microns) (this is important and we will come back to this later). Depending on which part of the world you live in will heavily impact the type of PM you come into contact with. For example, in the UK our primary source of PM is TRAP and industry, whereas in sub-Saharan Africa, a large proportion comes from combustion of fuel for heating and cooking.

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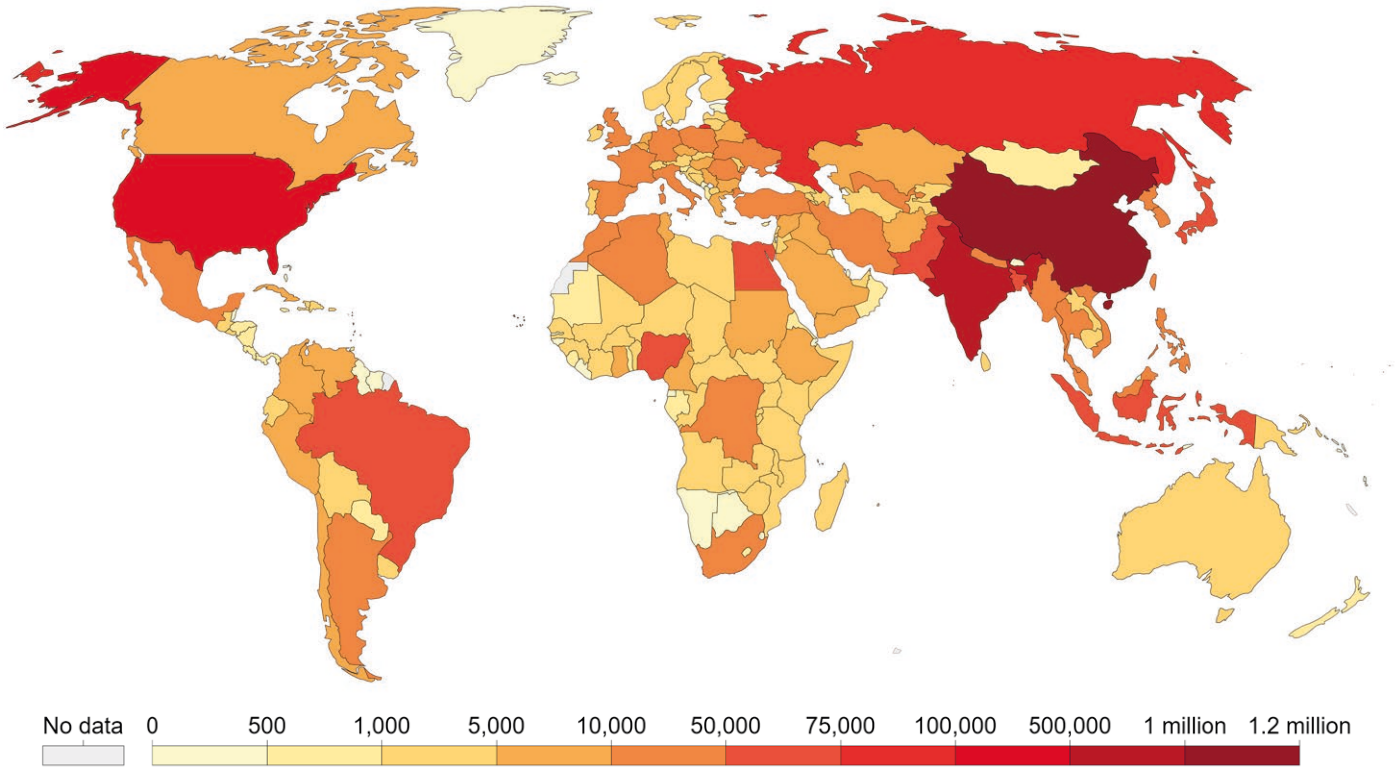

Figure 1. Number of deaths from outdoor air pollution, 2017. Data Source: Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018. [©OurWorldInData.Org. Licensed under CC BY 4.0]

How does air pollution get into the body?

This is relatively straightforward – we breathe it in and this is where the size of PM becomes important. Particles between 5 and 10 microns (PM_{10} but not $PM_{2.5}$) are most likely to be found in the tracheobronchial tree (the bigger upper airways), whereas small particles are more likely to penetrate further, even as far as the alveoli where gas exchange takes place (Fig. 2).

What happens to PM once it is in the lungs?

What happens after we breathe the pollutants in is the part where research is still taking place but there are some pathways that are becoming clear.

Once PM and carbon particles make it into the lungs they are met with the frontline cells of the immune system, specifically macrophages. Macrophages are phagocytes, they sit in the alveoli and on the epithelium, and when the PM arrives, they engulf it and initiate an inflammatory signalling pathway and cell cascade (Sijan *et al.,* 2015). This is confirmed by the ability to see carbon within airway macrophages (either collected by induced sputum or bronchoalveolar lavage) (Fig. 3).

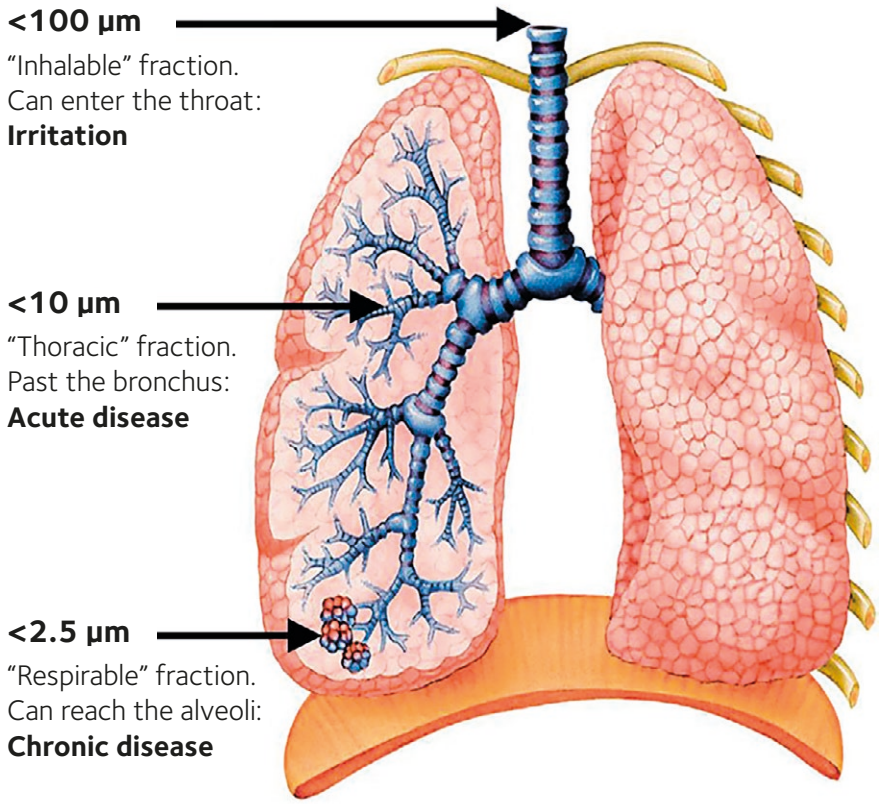

Figure 2. Relative deposition sites of particulate matter (PM) dependent on size. PM refers to particulate matter, size described in microns. For example, PM 2.5 µm refers to PM smaller than 2.5 microns. [Image Credit: Claire Horwell. Public domain from USDS.gov]

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"The physiological impact of exposure to pollutants can be seen throughout the life course, from the fetus to old age, and we now know that they affect almost every bodily system."

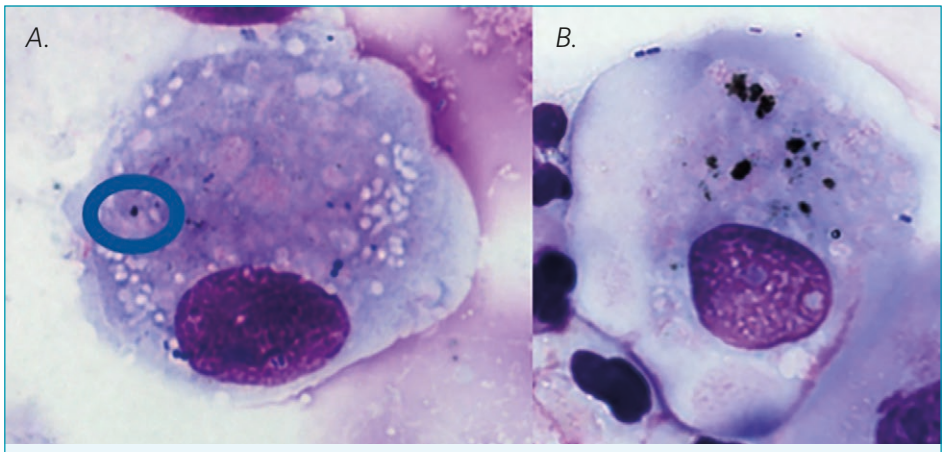

Figure 3. Airway macrophage black carbon. *A.* shows a small carbonaceous deposit, circled in blue, distinguishing it from bacteria also seen. *B.* shows multiple larger black carbonaceous deposits. Samples obtained using sputum induction; these are processed on cytospin slides prepared and stained with Hemacolor stain. Digital images obtained using a stereo-histology microscope (Mazurek Optical Services) at x100 magnification under oil. [Image Credit: Abigail Whitehouse]

This is clinically important. Multiple studies have found that not only does airway macrophage black carbon (AMBC) correlate with external markers of pollution exposure (modelled or personal monitoring) (Bai *et al.,* 2015) but also that it correlates with health effects. For example, Kulkarni *et al.* demonstrated an inverse correlation between AMBC and lung function in healthy children, where children with higher levels of AMBC have reduced FEV_1 (forced expiratory volume in 1 second) (Kulkarni *et al.,* 2006). These data are compatible with studies that have shown reduced lung function in children exposed to higher levels of air pollution such as in California where pollution is high (Gauderman *et al.,* 2002). Similarly, adults arriving from higher polluted cities from across the world outside of Belgium had significantly higher AMBC and lower lung function when compared with adult long-term residents of Belgium, where levels are relatively lower (Bai *et al.,* 2018).

At this point another phagocytic cell is important to mention, the Dendritic cell (DC). DCs are key sentinel cells that act at the intersection of innate and humoral immunity. They become activated after taking up foreign material through phagocytosis, macropinocytosis and receptor mediator endocytosis. DCs then degrade the phagocytosed material (Fig. 4), become activated (mature) and subsequently stimulate T-cells and release various cytokines, chemokines and other chemical mediators. These two processes alter the T-cell response potentially moving from a tolerogenic (resulting in regulatory T cell formation) state to an increased inflammatory state (resulting in a switch towards T helper type 2 cells), such as that seen in asthma. DCs are affected or influenced by what they are exposed to, with exposure to heavy metals, particulate matter or cigarette smoke all altering the function and maturation potential (and therefore the subsequent T-cell responses) of these cells (Pfeffer *et al.,* 2018).

So, what does air pollution do to health?

Air pollution exposure is the fifth leading risk factor for mortality worldwide with estimates of yearly attributable deaths now at 6.67 million (see Fig. 1; nearly 12% of the global total (Health Effects Institute, 2020). The physiological impact of exposure to pollutants can be seen throughout the life course, from the fetus to old age, and we now know that they affect almost every bodily system, with the respiratory system being the most obviously affected. Exposure to NOx and PM has significant effects on both lung development and lung function, with the effects starting *in utero* when the fetus is "indirectly" impacted due to placental insufficiency, a process in which the placenta is unable to provide adequate support to the growing fetus (van den Hooven *et al.,* 2012). Subsequently this results in adverse birth outcomes such as low birth weight and preterm delivery (Ha *et al.,* 2014), which are associated with PM exposure. These will affect lung growth and development and may have long-lasting impacts such as a predisposition to chronic lung diseases in later life.

Lung function has often been used as a marker of pollution exposure, with significant impacts on both FEV_1 and FVC (forced vital capacity) negatively affected by PM and NOx/NO_2 exposure (Hwang *et al.,* 2015; Tager *et al.,* 2005). When exposure occurs in childhood, those affected may never achieve optimum lung function potential for their height and sex. The Children's Health

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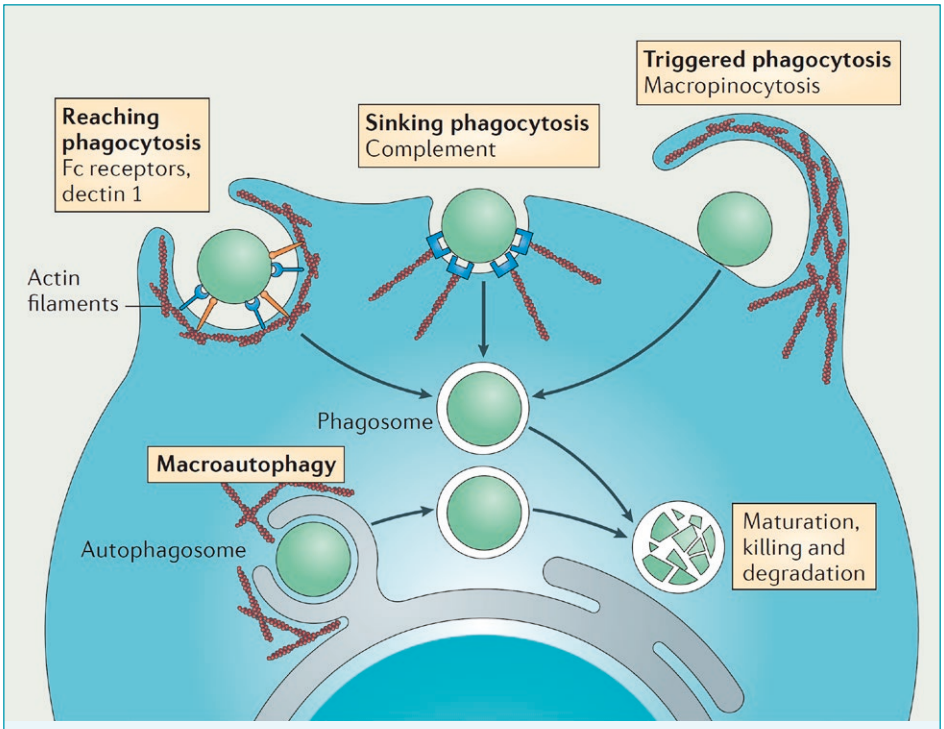

Figure 4. The various processes of phagocytosis. [© 2012 Macmillan Publishers Limited. Underhill *et al.*, 2012. DOI: 10.1038/nri3244]

Study found that the estimated proportion of 18-year-old subjects with a low FEV_1 (defined as a ratio of observed to expected FEV_1 of less than 80 percent) was 4.9 times as great at the highest level of exposure to $PM_{2.5}$ as at the lowest level of exposure across the studied areas in California (Gauderman *et al.*, 2004), which will then result in greater declines in adulthood.

The current evidence strongly suggests that pollution exposure results in more frequent asthma exacerbations, increased hospitalisations due to wheezing and respiratory symptoms and respiratory infections such as pneumonia. Meta-analysis studies carried out within the ESCAPE birth cohorts found significant associations between PM_{10} and NO_2 and pneumonia prevalence, as well as increased risk of otitis media (infection of the inner ear) (MacIntyre *et al.*, 2014). These effects are probably not only confined to outdoor air pollutants since Lin *et al.* found that gas cooking increased the risk of both asthma prevalence and risk of wheezing within a meta-analysis of 41 studies (Lin *et al.*, 2013). This may then suggest that adequate ventilation in kitchens is important, particularly when using gas cooking or when there is a significant particulate release such as through the cooking of toast and roast dinners.

Further health effects include exacerbation of existing cardiovascular disease and increased risk of myocardial infarctions, heart failure and stroke. There is significant evidence that pollution is associated with cancer and there is emerging evidence that exposures may also contribute to type 2 diabetes, Alzheimer's disease and potentially autism incidence.

Well, what should we do?

With overwhelming evidence of harm, now is the time to declare that our priority is to reduce air pollution exposure, particularly for those most as risk, children. It is clear that to reduce exposure a buy-in from governments and policy makers is required, to increase funding for pollution-lowering policies such as low emission zones and bans on polluting vehicles. However, large-scale interventions will take time to have impact, so we need to promote small-scale pollution-reducing strategies that we can do in our own homes (more research is needed to look at effectiveness of these). Similarly, we need to promote how to reduce our own exposure through avoiding pollution hot-spots and increasing time spent in green spaces. Now is the perfect time to start, pollution levels were significantly affected by the coronavirus lockdown in the UK, with significant reductions noted by Defra of a 40% reduction in NOx levels. However, they are already returning to pre-lockdown levels.

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Long-lasting cellular imprinting

Performance hacking towards the Olympics?

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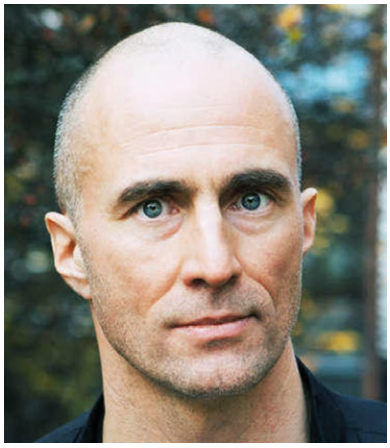

Professor Jo Christiansen Bruusgaard

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Muscle memory is a term that for decades has been associated with the ability to learn specific motor tasks. Repeated practice enables complex muscle contractions like playing the piano or riding a bicycle to be performed more or less automatically, but the term is not very precise, as it really involves changes that occur in the brain, and not in the muscle cells. However, during the last decade several findings indicate that the muscle cells themselves have the ability to "remember" former greatness.

A cellular muscle memory

Muscle cells are unique in several aspects compared with other cells, but most prominent is their immense size and the fact that they contain hundreds if not thousands of nuclei (Fig. 1). More than 10 years ago we, together with several other researchers in our group, found that when subjecting rodent muscle to mechanical overload, the addition of new nuclei to the muscle cells preceded muscle growth, and remained in the cells even after severe muscle atrophy (Bruusgaard *et al.*, 2010). Furthermore, muscle growth induced by anabolic steroids in mice added more nuclei in a similar manner, and after a long period without exposure to anabolic steroids these muscles appeared to have a significant growth advantage when subjected to mechanical overload (Egner *et al.*, 2013) (Fig. 2). We described this phenomenon as a cellular form of muscle memory residing in the muscle cells themselves, with the number of muscle fibre nuclei (or myonuclei) as a "memory storage unit". The hypothesis that the number of myonuclei represents an advantage for muscle growth has generated some controversy (McCarthy *et al.*, 2017), although the absolute need for myonuclei in order for muscle fibres to complete their postnatal developmental growth has recently been verified by transgenic mice that leave satellite cells fusion-incompetent. By inducing the transgene at different developmental timepoints, satellite cell fusion can be stopped and the number of myonuclei specifically titrated (Cramer *et al.*, 2020).

Given the finding that steroids had a long-term effect on the muscle's ability to grow in mice by increasing the number of myonuclei, we thought of ourselves as "the knights in shining armour" of antidoping. And indeed, shortly after the Egner *et al.* paper (2013) the exclusion period for testing positive for steroids was raised from 2 to 4 years (World Anti-Doping Agency, 2015). However, it was soon pointed out that if it was true that the effect of anabolic steroids lasted long after the substance and metabolites were cleared from the blood, athletes could be "primed" at a young age before they entered professional competition - a way of hacking your body without the risk of being caught.

Epigenetics and cellular memory

Research during the last decade has also investigated the phenomenon of a cellular memory in lieu of epigenetic alterations.

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Epigenetics is defined as non-sequence structural modifications of DNA and/or histones that alter patterns of gene expression, and diverse environmental stimuli can provoke epigenetic responses in many different cell types that can last for decades, and even be transferred to offspring, one example being maternal nutritional status (Vineis *et al.*, 2017). Current evidence also supports a long-lasting exercise-induced epigenetic memory in skeletal muscle (Beiter *et al.*, 2020), whereby previous strength training, leading to long-lasting changes in DNA methylation patterns, aided future muscle mass gains in humans. Thus, all environmental stimuli that can lead to short-term cellular adaptation can lead to epigenetic imprinting that bear the potential of a long-term cellular memory. It even provides a possible epigenetic explanation for the idea of athletes breeding athletes.

Performance-enhancing drugs

Based on the current knowledge about cellular muscle memory, together with evidence for an epigenetic memory in response to a number of physiological stimuli in different cell types, establishment of a cellular memory after abuse of performance-enhancing drugs is also likely. As environmental stimuli can lead to epigenetic memory in haematopoietic stem cells (makers of red blood cells) (Vineis *et al.*, 2017), a similar epigenetic memory response to erythropoietin abuse seems plausible. For steroids it has been established that testosterone has the potential to induce epigenetic programming in mice (Dkhil *et al.*, 2015), and that strength exercise induces epigenetic muscle memory in humans. In our opinion this makes it plausible that testosterone can lead to an epigenetic memory in skeletal muscle.

Long-lasting effects in humans

Do performance-enhancing drugs give a competitive edge in a long-term perspective for elite athletes? Indeed, anabolic steroids induce both increases in strength (Bhasin *et al.*, 1996) and myonuclear number (Kadi *et al.*, 1999), but few studies have been able to investigate this in a controlled manner. However, a hint towards long-lasting effects appears in the doping programme of the German Democratic Republic government, starting in the mid-60s. Here, the first documented case of androgenic doping of a woman is described by Franke *et al.*: "*after 4 years of systematic androgenization, her basic strength level even when not taking the drug had also increased*" (Franke and Berendonk, 1997). It should be noted that some of this retention of strength might be a result of the muscle's ability to keep much of its gained size (Psilander *et al.*, 2019), and not in a muscle memory phenomenon *per se*, but this would still represent a long-lasting performance effect.

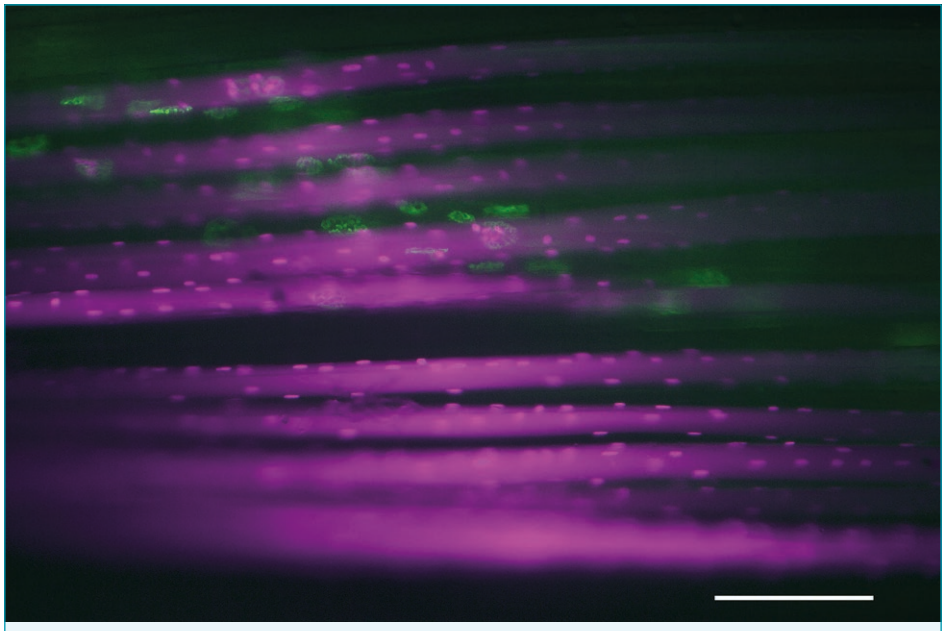

Figure 1. Muscle fibres are long, cylindrical cells and contain multiple nuclei. The image shows acetylcholine receptors in the neuromuscular synapse (green) and muscle nuclei (magenta) in a living mouse. A total of 10 muscle fibres on the muscle surface segments are labelled. The discovery that muscle nuclei are permanent during periods of atrophy rested on our lab's ability to label muscle nuclei *in vivo* and follow them over time. Scalebar is 100 mm. [Image Credit: Jo C. Bruusgaard]

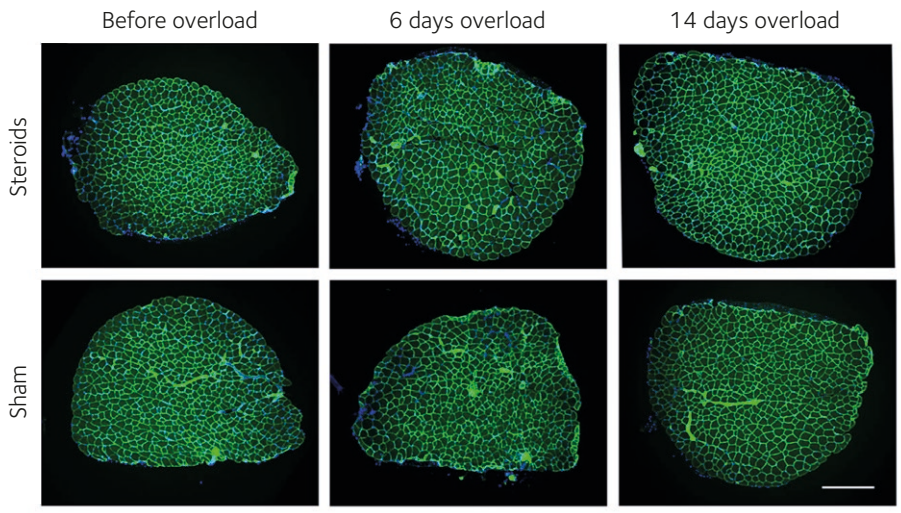

Figure 2. After a 3-month detraining period, the cross-sectional area (encapsulated by dystrophin in green) in the extensor digitorum longus muscle of female mice is similar between groups (left column); however, the myonuclear number (counted by DNA in blue) remains 28% higher in the female mice originally administered anabolic steroids at the beginning of the experiment. Subsequent overload training after the 3-month period increases the cross-sectional area in the steroid group by 31% versus 6% in the sham group by day 6 (middle column), and remains 20% higher in steroid versus sham controls by day 14 (right column). [© Egner *et al.*, 2013]

"Epigenetics is defined as non-sequence structural modifications of DNA and/or histones that alter patterns of gene expression."

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Hacking your performance

With recent findings on muscle memory as the backdrop, it is timely to debate whether early use of performance-enhancing drugs can result in a permanent advantage in exercise adaptability, giving that extra edge needed to outperform others in elite sports. If advantages from the intake of performance-enhancing drugs can be present long after its traceability, it leads to dystopic consequences for elite sports: one can use performance-enhancing drugs before even being considered for an anti-doping programme, involving minimal risk of getting caught, and stand on top of the podium in the Olympics much later. In elite sports, the margins are often small, and a 2% improvement in performance can be the difference between winning and coming last in a 100 m race.

Considering this, even a small residual effect of former doping, whether it resides in an epigenetic imprint, increased number of nuclei or retained muscle mass, the result is the same: former doping could lead to an advantage even long after the doping took place. In light of these observations, even longer exclusion periods should be considered, and novel methods with the potential to detect previous doping use should be explored.

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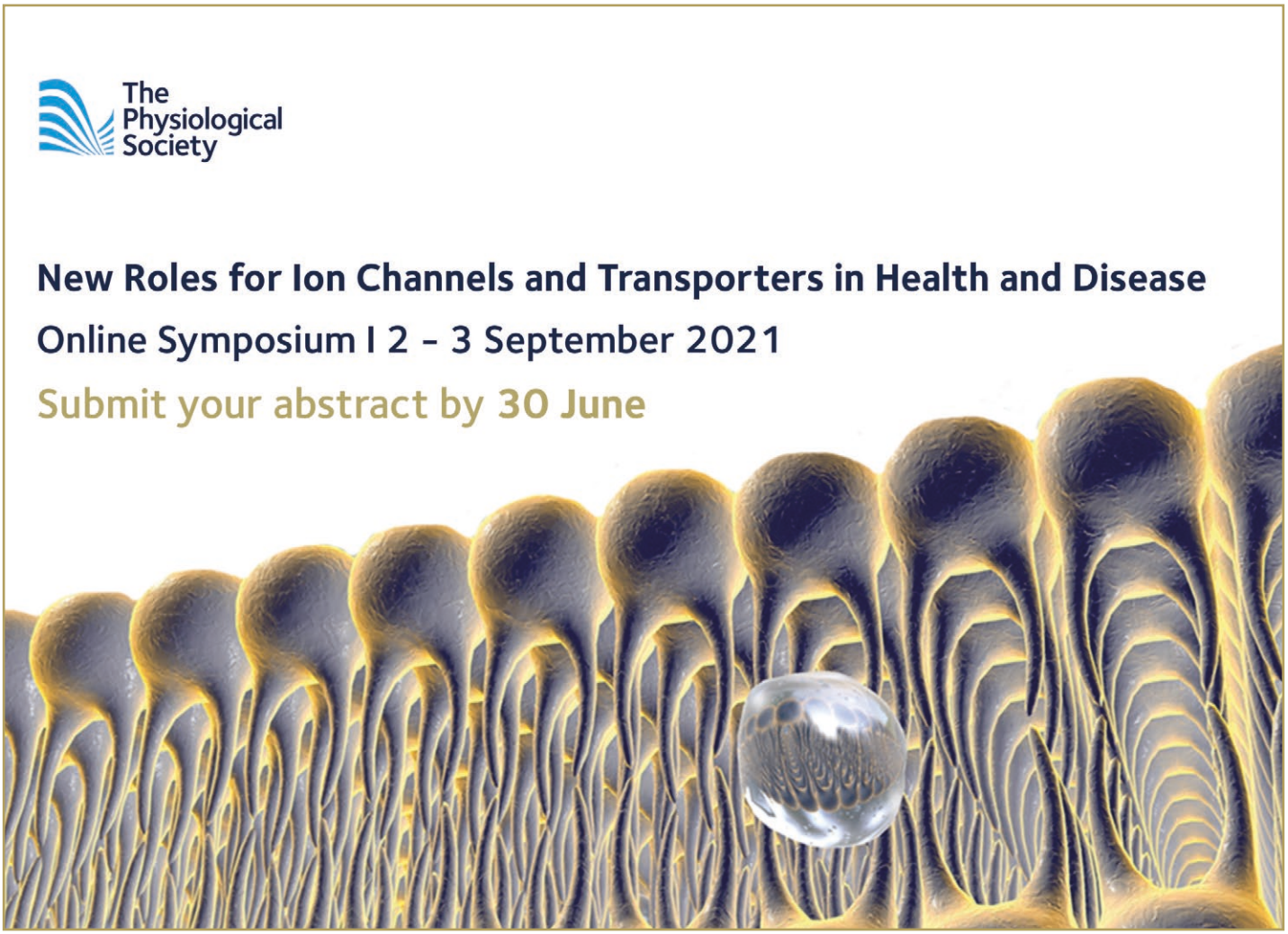

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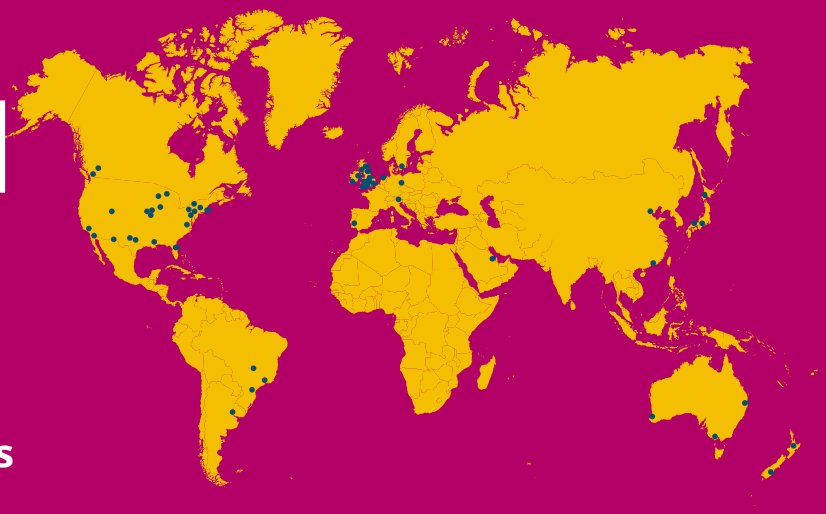

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Meeting preview

Physiology 2021

12 – 16 July 2021
Held online

Every year, our Annual Conference is a flagship event with first-class physiology, exciting Prize Lectures and unmissable networking opportunities. Physiology 2021 is no exception.

This will be an innovative online event for members and the broader physiology community, with hundreds of fellow physiologists from around the world joining us 12 – 16 July for the best and most exciting in current physiological research.

Across the five-day scientific programme, you will hear from world-leading physiologists discussing their latest research. With our inspirational Prize Lectures, symposia and workshops, our conference will feature physiology from across our Scientific Themes.

"The Annual Conference is the highlight of The Society's year. Physiology 2021 will be my first annual conference as President and I'm looking forward to welcoming physiologists from across the world for a truly global celebration of cutting-edge science." – Professor David Paterson, President of The Physiological Society and Head of Department, Physiology, Anatomy & Genetics at the University of Oxford, UK.

Although continued effects of the COVID-19 pandemic mean we are not able to meet in Birmingham as originally planned, the technology for this online event will provide opportunities for real-time feedback and discussions, and small-group networking, which is often missing from online events.

All scientific talks will be recorded and available on demand in the platform, allowing you to watch multiple sessions up to 30 days after the conference has ended. You will also be able to connect with people before, during and after the conference.

"Physiology 2021 is an incredibly important conference for all physiologists. The online platform makes it really easy to network with colleagues from across the world. After what has been a tough period for us all, I'm looking forward with pleasure to the community coming together." – Dr Sue Deuchars, Chair of Conferences Committee and Director of Research, School of Biomedical Sciences, University of Leeds, UK.

A key component of any Society meeting is the oral and poster communications showcasing the latest research often from early career researchers. There are 126 oral communications and two sessions of ePosters at the conference. Another positive for this online conference is that the ePoster showcase, with its multimedia-rich ePosters and three-minute flash talks, will be available before and after the conference too.

"The Society's conferences are always a lot of fun as well as great for getting early eyes on research. Thanks to The Society for holding this online as it would have been a shame to let another conference slip away this year," Bernard Drumm, Dundalk Institute of Technology, Ireland.

Registration is still open and closes on 30 June.

www.physoc.org/physiology2021

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Does the country matter? Research and career of a Brazilian Fellow Member

Professor Elaine Del Bel

University of Sao Paolo, Brazil

In the 1980s, I had the opportunity to do my postdoc in England, in Manchester, where I learned a bit about the British people. I learned to enjoy scones, Irish butter, and most of all, English tea!

Back then, the first member of The Society I met was Professor David Brown, and I went to my first Society conference under his tutelage. I remember I asked him: if The Physiological Society holds joint congresses, why has there never been a joint meeting with the Brazilian Society of Physiology? That was the magic question! Several successful conferences were organised after this between the two societies.

Generous travel grants from The Society meant that I could attend conferences almost every year. Some faces became familiar to me, from Society staff to physiologists. In the last few years I was invited to give talks, which terrified me at first but also made me very proud.

It feels like I then suddenly became a Fellow Member of The Society! I see this as an opportunity to continue to spread the word about what The Society has brought me, personally and academically. In addition to outstanding science and the possibility to have in-person interactions with other scientists, The Society showed itself to be open, inclusive, and generous. This is why I was, and still am, delighted to be part of this community.

My scientific origin story: physiology in Brazil

I think I was born a nerd, but I certainly did not have a trajectory for my life laid out. I took the opportunity to do a postgraduate degree where I dedicated myself entirely and managed to find myself.

I have no recipe for success, but what I did was work hard, while also taking care of my mental health. I have always made time for reading (devouring books in the library), enjoying cooking and taking care of plants, in my house and garden. The birth of my daughter, and the unconditional love I had for a little being, gave me another reason for balance.

One of the biggest barriers for me was the English language. The time spent in England was of paramount importance to overcome the difficulty I had with speaking the language.

Lab-Group. From the left to the right, standing-up, Carol, Keila, Glauce, Mariza, Elaine; sitting below, João-Francisco, Fernanda, Bruno and Celia.

As I connected with more people, scientific partnerships started to appear, during meetings and courses, because of friendships and mutual scientific interest. The postdoc and then the international congresses, the organisation of visits to laboratories in Germany, England, France, and the USA, helped to open doors.

Foreign researchers eventually managed to get out of their comfort zone and came to see a little of the science that is done in countries like Brazil. They learnt that there is a struggling and intelligent population.

Our challenges in Brazil are many and fundamental, such as inadequate funding and inconsistency in the value that the government places on education and science.

We are a nation in which there isn't gender equality nor equality for other marginalised groups. There are powerful prejudices along the lines of race and socioeconomic status. This is a matter of justice and rights and we are still far from solving it.

But, the community is strong and united, and still young! You learn to do good scientific research even if invited to the seaside by the sun shining outside. We often have a natural instinct for working with animals, which is not easy. Despite our difficulties, we have been able to maintain research excellence in physiology, training a new generation who will be able to continue to understand scientific advances.

My current research

I have a passion for imaging different microstructures (such as neurons and glial cells) that make up the central nervous system. The shape of the cells is art to me; they are vigilant and change in response to the physiological conditions of the environment. Observing them can teach us a tremendous amount.

I have been studying Parkinsonism in rodents, induced by lesions of dopaminergic neurons. I analyse the effect of drugs that may protect these neurons.

Recently, an antibiotic called doxycycline (6-deoxy-5-hydroxytetracycline) has emerged as a potential treatment for Parkinson's disease. Our group of Parkinson's disease researchers made the discovery while modelling the disease in mice.

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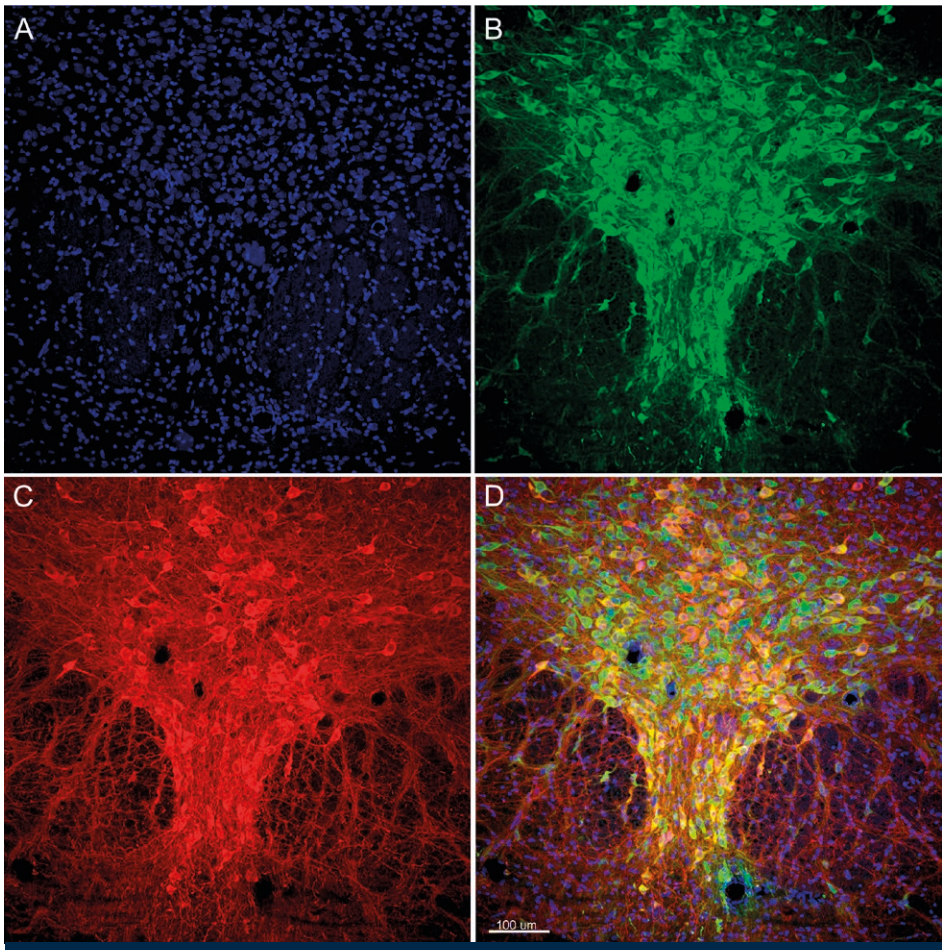

Photomicrographs of double-immunostained sections from the rat raphe nuclei presenting neurons fluorescent signals. DAPI-labelled cell nuclei (A-blue); Tyrosine hydroxylase (B-green); neuronal nitric oxide synthase (C-red); D- Merge (co-localisation- yellow). Credit: Professor Elaine Del Bel.

We noticed that only two of the 40 mice that were administered 6-hydroxydopamine (6-OHDA) developed the motor features of Parkinson's disease while the rest remained healthy. We realised that this was because the mice had mistakenly been fed chow containing doxycycline. Doxycycline is second-generation tetracycline antibiotic increasingly being used in neurodegenerative diseases treatment due to their anti-inflammatory features. Previous evidence demonstrated doxycycline protection to dopaminergic neurons.

Our hypothesis was that it might have protected the dopaminergic neurons from the toxic effect of the 6-OHDA. We repeated the experiment, adding another group of mice, which were given doxycycline in low doses by subcutaneous injection and fed on normal food. Both groups demonstrated that sub-antibiotic doses of doxycycline have a statistically significant neuroprotective effect.

An accidental discovery of this sort can be a lucky thing, especially since doxycycline has been shown to be safe, and is an FDA-approved agent.

In view of the long-established and safe clinical use of tetracycline, we propose that these drugs could be an adjunctive therapy to the dopamine precursor treatment called levodopa (L-Dopa) to prevent the development of dyskinaesia.

Dyskinaesias are abnormal involuntary jerking movements that appear when plasma and brain levels of L-Dopa are high. More than 50% of patients will begin to develop motor fluctuations and dyskinaesia between 5 and 10 years after the start of L-Dopa therapy, with 20%–30% developing dyskinaesia after less than two years.

There are no cures for Parkinson's disease and the treatment is simply symptomatic. Dyskinaesia is a highly disabling condition for the patient.

We continue to investigate this drug and others that can be used to treat Parkinson's disease and the side effects that can result from existing treatments.

My career today

A crucial moment in my career was when I decided that I would try to do what really motivated me to be alive, which was learning and studying. I quit a stable job and chose to live through an era of career uncertainties. The path was hard, with hesitation, tumbles, and mishaps.

But I got where I am, a professor at one of the best universities in Brazil, even though I am a woman in Latin America, from a family of workers, with no academic background. It still feels unbelievable sometimes.

I do wonder what chances I have to be a protagonist in the competitive field of brain physiology. I really do not know. What I do know is that I can give local people the opportunity to learn the language of science, so to speak.

I can encourage the young people who come to me. I hope to show them that even with all the problems we have in Brazil, we cannot turn off the light and close the door. Courage and struggle can bring us an inner peace and a life that is "rich" in a way.

We are going through an extremely challenging time, both locally and globally. In this very difficult, ungoverned country, where it is still debated whether or not vaccines have value, whether scientific knowledge is worth anything (and whether the earth is flat!), social differences have come even more into the foreground in the last year.

The dismantling of public universities and scientific funding is now reaching an unsustainable degree. The difficulty in fighting back effectively makes me feel powerless and incapable.

Despite being exhausted from the sadness and the horror of the moment in my country, I am observing the changing seasons in nature, cooking more, and working from my veranda, somehow, managing to enjoy life. Despite all this, I continue guiding students, having daily or weekly virtual meetings, and discussing science. Because life will go on.

"I have no recipe for success, but what I did was work hard, while also taking care of my mental health."

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Crossing the barriers in health care education

Dr Alison Wood

Lecturer in Nursing, Division of Nursing, Queen Margaret University, UK

Dr Colin Chandler

Lecturer in Life Science, Nursing Studies, University of Edinburgh, UK

A knowledge of the biosciences, and physiology in particular, underpins practice in many healthcare areas. How as physiologists can we support this area of learning and what is needed to support healthcare practitioners in their pre-registration learning, ongoing CPD and advanced professional learning?[1]

As part of a David Jordan Teaching Award, an opportunity to meet with other nurse educators and discuss the complex topic of physiology within the nurse education curriculum was welcomed. Eight educators met to thrash out the start of a physiology curriculum; however, in doing so we also shared the challenges we face when embedding these into a course or programme.

The purpose of this study was to provide guidance to educators, reduce variability, and set a benchmark in terms of level and breadth for the foundational physiological knowledge that supports professional development and safe patient care.

However, it is clear that within pre-registration nurse education (degree level leading to professional registration), and other allied health degrees, the time allowed for physiology alongside other biosciences continues to be low. For some nurse programmes, as little as 200 notional equivalent study hours within a nursing degree for all biosciences (10 European Credit Transfer System (ECTS) credits or just over 5% of a three-year degree).

Physiology learning outcomes for nurses

The project funded by The Physiological Society provided a clear definition of the relevant physiological knowledge that is required by nurses to support their clinical practice at registration and completion of their degree.

This consensus-driven identification of 177 core learning outcomes were developed to define the key physiological concepts on which nurses will build throughout their future careers and professional development.[2]

These core outcomes are needed as nurses (and healthcare professionals) need to be able to articulate to colleagues, individuals and families what is going on in front of them when caring for an unwell individual and their families. This can be particularly important in times of remote working, in online and telephone consultations, where the nurse is providing care with or without direct support.

This work parallels other initiatives looking at healthcare curriculums including The Physiological Society's own physiology curriculum for medical students, and in other disciplines such as anatomy.[3,4]

To see the importance of physiology underpinning the curriculum let's consider some clinical scenarios to show why physiology concepts are key.

https://doi.org/10.36866/pn.122.42

Scenarios	Physiological importance
Venepuncture and the principles of coagulation	Understanding the clotting mechanism and its importance in haemostasis
The selection of a dressing depending on the level of wound healing	Understanding inflammation and necrosis to identify appropriate treatment
Choice of injection technique and administration of medicine dependent on muscle or skin layers	Understanding absorption and drug delivery routes, as well as the variation of pain with the choice of needle size
Prevention of infection	The nature of the microbiota and their interaction with the human body in health and disease
Arguing why a maintained blood pressure does not necessarily mean the patient is not haemorrhaging!	An understanding of blood pressure control and physiological shock

Table 1. Clinical scenarios illustrating the importance of Physiology Concepts in Nursing Practice

"This work parallels other initiatives looking at healthcare curriculums including The Physiological Society's own physiology curriculum for medical students, and in other disciplines such as anatomy."

Clinical scenarios illustrating the importance of Physiology Concepts in Nursing Practice (Table 1)

Many practitioners qualifying at degree level or higher are not trained as academic scientists, but as users of knowledge to understand and support their practice. They need to be able to communicate to their patients and their families what is happening to enable informed and shared decision making on their care.

The COVID-19 pandemic has highlighted that nurses, alongside other allied health professionals, are key to patient care, safety and in maintaining NHS services. Staff being redeployed to intensive care units from various parts of the health service highlight the need for nurse degree education to ensure a foundation of core concepts including physiology.

Working together

Interacting with these professional groups is an exciting and educative experience for a physiologist. The students bring experience, insights, and questions from practice, but some barriers exist in this collaboration.

Our different disciplines may not share the same language; even the same words may have different meaning in the different contexts. This requires a mutual respect and ongoing dialogue to resolve confusion.

As adult learners, students bring their experience into the setting and this needs to be used as a resource and clinical context to the topic; they are ready to learn and enthusiastic but need to be able to see the relevance and application of their learning.

One of the real challenges for educators within the healthcare professions is the variation of education level at the beginning of their healthcare degree. We are sure readers of *Physiology News* would agree that it is key to have the physiology principles of good health as an early part of a degree so that students can then understand as they progress and develop the principles of ill health or disease. When faced with a class of new students, all enthusiastic but some having very little science knowledge already in their arsenal, how can we as educators take all the students with us on this journey through physiology?

For many learners the challenge may be to engage with the initial scientific concepts that can open the door to greater understanding. Supporting learners to cross these threshold concepts is both a challenging and rewarding aspect of working across the scientific and clinical disciplines.

Healthcare, like physiology, does not stand still in its knowledge base but is continually developing. Often it is more important to understand and grasp the fundamental concepts, as a platform to fit specific and relevant new information. This also acts as a basis for future learning and understanding as knowledge develops in their practice.

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Moving forward in collaboration

This past year has been one of rapid adaptation both in academia and in healthcare practice. Redeployment to areas of high need has been common in healthcare, and a shift from face-to-face teaching to online delivery in academia has happened.

These have presented challenges and opportunities. As we emerge from the pandemic this is a great time to think about how we can develop and support practice learning in new ways. Can we engage practitioners at all levels in learning using many of the resources we have developed over the last year? To summarise, the issues we face are getting the level of study and detail right for learners in their professional practice. We also need to have a clear idea of what is important in a topic to understand both the physiology and the clinical relevance. But the benefits for working together are huge. The opening up of opportunities for physiologists to engage with healthcare professionals, both students and practitioners, by identifying real-world practice issues that are being faced and generating new questions that can lead to new areas of research.

This requires an open mind, willingness to engage in conversations and different disciplinary approaches. It requires a recognition that healthcare is person-centred, as individuals or patients are of key importance in decision making and engagement, and it is their lives on the line and their healthcare experience.

We also need to understand how people use and learn from online material. It is best delivered in small chunks, related to practice and engaging with student experience.

Can we share resources that are under Creative Commons licences, such as: lectures (recorded – preferably short and engaging), animations, activities, practicals, virtual reality (VR) resources, or clinical scenarios and case-based discussions.

The recent events and changes to how we as practitioners and educators engage with learning and learners have provided us with an opportunity to relook at what we do and how we should do this better in the future.

Collaborative working of physiologists and healthcare educators and learners can provide a wealth of opportunities. It can be a great way to bring your science to life, relating it to the real world of healthcare and demonstrating its impact to the wider public.

> "Collaborative working of physiologists and healthcare educators and learners can provide a wealth of opportunities."

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Nursing students performing cardiopulmonary resuscitation (CPR) within a simulation exercise.

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STEM for Britain 2021: Tackling trauma one organ at a time using a reverse translational approach

Nikita Patel

Queen Mary University of London, UK

I had the great privilege of sharing my research at this year's STEM for Britain event and presented a poster entitled "Tackling trauma one organ at a time using a reverse translational approach".

stemforbritain.org.uk/wp-content/uploads/2021/03/NIKITA_PATEL_2021_POSTER.pdf

Someone dies from an injury every six seconds. Physical injuries, which may be blunt (such as road traffic accidents) or penetrating (such as stabbings and shootings), are a serious public health problem. They are the leading cause of death and disability in those aged under 44. Globally, there are more than 5 million trauma-related deaths each year. This is nearly double the number of fatalities that result from HIV, tuberculosis and malaria combined. Unfortunately, the problem is only growing.

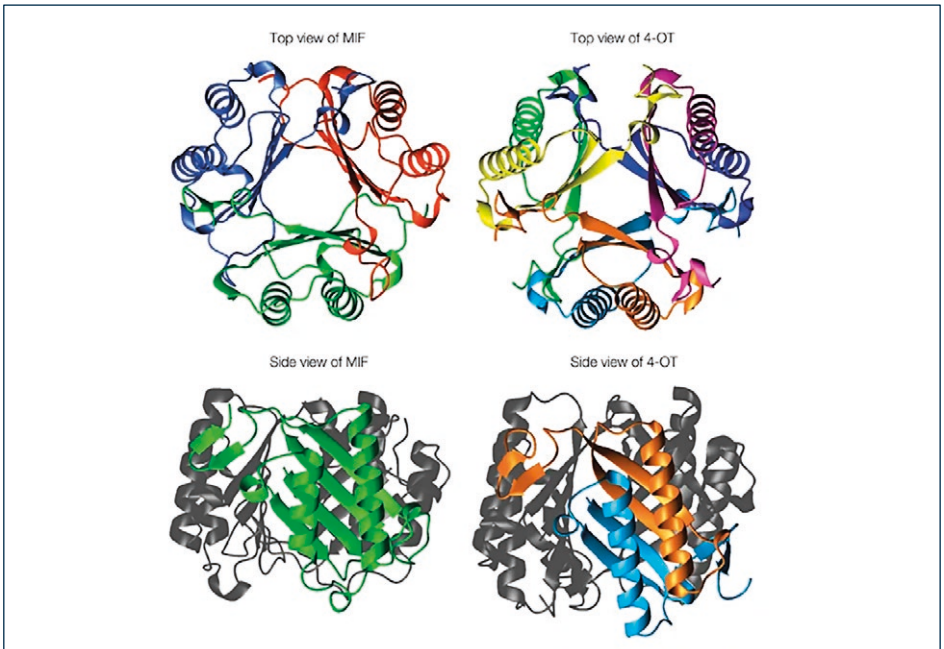
Trauma patients who survive the initial injury often develop multiple organ failure at a later stage. This is due to haemorrhagic shock (severe blood loss) and the detrimental actions of pro-inflammatory molecules, which circulate around the body. One molecule of particular interest is macrophage migration inhibitory factor (MIF).

MIF is a pleiotropic cytokine with chemokine-like properties known to modulate the inflammatory response and is found at low levels in the blood of healthy people. Previous research has shown that levels of MIF increase after trauma and other diseases like sepsis and acute respiratory distress syndrome (ARDS). I therefore wanted to investigate how MIF contributes to disease in trauma patients and examine whether by blocking MIF there would be a decrease in organ failure in a rat model.

The first step was to measure MIF levels in the blood serum of trauma patients at different timepoints (emergency room, day 2, day 5 and day 7). I found that serum MIF levels were the highest in the emergency room. The levels decreased over time but still remained higher than healthy volunteers even seven days after the initial injury. I also found that the higher the MIF levels on admission, the longer the patients had to spend in ICU and hospital overall.

Usually, animal research occurs before human research but in this case, my findings from the trauma patients helped to inform my future experiments with rats. This can be classified as a reverse translational approach.

I used a rat model of haemorrhagic shock, which simulates what may happen to a trauma patient. I assessed whether ISO-1, an experimental drug that blocks MIF, would reduce organ injury and dysfunction. When compared with healthy rats, the vehicle (placebo)-treated rats showed a significant increase in renal (kidney) dysfunction and hepatic (liver) injury; as measured by blood serum parameters. In contrast, rats treated with ISO-1 displayed a significant reduction in both renal and hepatic damage.



3D structure of MIF illustrating the homotrimeric composition. [© 2003 Nature. Calandra and Roger, 2003. https://doi.org/10.1038/nri1200]

Taken together, my results from the human and rat studies highlight that MIF levels can predict how quickly a patient may recover and blocking MIF could be a potential new therapy. The latter is particularly important as there are currently no treatment options to prevent organ failure.

Despite the harsh reality that it is impossible to eradicate trauma, these findings could greatly impact patient quality of life whilst simultaneously decreasing the burden on the healthcare system.

I was absolutely thrilled to not only receive The Physiological Society Prize but also the Gold Medal in the Biological and Biomedical Sciences category! I entered STEM for Britain as I thought the event was a great opportunity to disseminate my research and raise awareness in the field of trauma and haemorrhagic shock, given its high prevalence in society. The ability to communicate and discuss science with a lay audience is an important skill to have, just as important as the research quality and integrity.

Hopefully I've emphasised to people that trauma and haemorrhagic shock research is important and should be studied. The awards may help to attract more funding as, unfortunately, less than 1% of all medical funding is spent on trauma research despite its high incidence. The event and awards have also motivated me to seek out additional opportunities to share my work and further down the line, post-PhD, I would be keen to stay involved in science communication and public engagement whilst working in research and development.

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Re-purposing a clinical device for the classroom: The tale of teaching cardiovascular physiology with ultrasound

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The David Jordan Teaching Award is a grant to enable awardees to carry out a piece of educational research or to develop an educational resource that is relevant to physiology. This award recognises innovation in physiology teaching.

In 2015, we used it to purchase a portable ultrasound system. Our aim was to investigate the effectiveness of ultrasound technology as a tool for teaching cardiovascular physiology, a novel use of ultrasound at the time.

Previously we used more primitive and bulky machines (usually donated by clinical colleagues) that required extensive technical expertise to operate (referred to in the ultrasound literature as "knobology") to achieve mediocre images. However, the award of £10,000 meant that we could purchase a basic but modern machine that was easy to operate but produced good-quality images. This use of ultrasound is quite separate from using it as a clinical tool that focuses on how to conduct various examinations.

Rather, we use it to image the heart and blood vessels as they undergo physiological changes and have found it works incredibly well for underpinning the understanding of some core physiological concepts.

Informally, even when colleagues see how ultrasound imaging can be used to aid physiology teaching of, say, the Frank–Starling law of the heart, or the consequences of a supine posture with legs raised on venous return,[1] they are struck by the immediacy of such demonstrations and how obvious it is to apply the technology in this way.

It is also immensely popular with students. In the first stages of our project, we used ultrasound imaging to bring to life the theoretic basis of cardiac physiology in a laboratory environment through live demonstration. Chris was trained (many years ago!) in cardiac ultrasound techniques in his former life as a clinical physiologist in cardiology and therefore performed the image analysis. Student satisfaction and enjoyment of these practicals was measured by Likert scores (where statements about the practicals were awarded a score from 1 to 5 depending on whether students strongly disagreed with the statement (scoring 1) or strongly agreed with the statement (scoring 5) with neither agreeing nor disagreeing scoring 3). Their learning was assessed by self-perceived understanding before and after the practical.

The authors posing with a portable ultrasound device.

Students were asked to measure cardiac dimensions in systole and diastole and thereby derive, from first principles, important measures of cardiac function such as stroke volume (SV), ejection fraction (EF), and cardiac output (Fig. 1). We then were able to demonstrate how SV and EF increase after a subject performed a brief period of exercise, which led to discussions about factors that affect cardiac performance.

In self-reported results, 52% of students stated that they understood the Frank–Starling Law better after the class, 94% of students felt that performing calculations helped their understanding of the underlying physiology and 89% of students stated that they enjoyed the teaching session.

Ultrasound enables students to view and appreciate vascular physiology including venous phenomena such as the role of venous valves in ensuring blood returns to the heart, venous collapse of the jugular vein to measure central venous pressure (important in cardiac function), the various phases of the pulse in the internal jugular vein (reflecting right atrial pressure) and how it is affected by changes in intrathoracic pressure induced by speech and the Valsalva manoeuvre. 84% of students strongly agreed that ultrasound enabled them to see the clinical application of understanding venous pressure.

The successful execution of the first series of experiments resulted in three poster presentations at the main meeting of The Physiological Society in Dublin in 2016. On the back of this, we won a local rapid-fire presentation teaching award and we published two peer-reviewed papers in *Advances in Physiology Education*.[2,3]

The final phase of the investigations is underway with a paper currently in preparation on the change in performance in simple "Single Best Answer of 5" examination questions before and after practical classes, comparing conventional classes with "enhanced" practicals using ultrasound machines to illustrate the concepts.

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The preparation of this manuscript has illustrated the difficulty in assessing deep learning by means of simple before-versus-after examinations, with deep learning being predicated on a prolonged and enthusiastic engagement with the material, with the results being inconclusive. Perhaps, assessing enthusiasm and engagement is more appropriate in this arena, as what we aim to enhance is the more subtle and indefinable property of enthusiasm, passion and engagement with the topic.

These thoughts are reflected by other pedagogic researchers such as Professor Ian Turner from the University of Derby, UK, who is developing interesting ways to "gamify" classes using videos/animations, visualisers, theatrical props (termed 3D display) and lecturer interaction to make them more theatrical, challenging and fun.[4]

The question "how do we measure learning after a two-hour class" may indeed need to be replaced by the more interesting question "how do we objectively measure fun".

This need to enhance deep learning and engagement by making classes more theatrical and interesting has led us down some interesting pedagogic pathways since receiving the David Jordan Teaching Award.

Directly out of the contemplation of the results of the last series of experiments came a collaboration with the Department of Drama in Queen's University Belfast and Dr Paul Murphy, on enhancing physiology tutorials by using acting students to play the part of patients. This nascent research has already been presented at the Aberdeen meeting of The Physiological Society (2019) and has been the subject of an invitation to the Mind Reading 2021 conference in Dublin on collaboration between artists and scientists.

So, although we continue to document the uses of ultrasound as a teaching tool and investigate its uses in the teaching of both anatomy and physiology, the David Jordan Teaching Award has led the investigators down other paths, which are proving fruitful and challenging.

The David Jordan Teaching Award was a godsend for us, as there is very little money available for education research, and what little there is has to go around all educational sectors, not necessarily physiology-related.

On a personal level, Chris knew Dave Jordan as a colleague and a mentor during his PhD, and without Dave's initial encouragement to consider lecturing as a career, he may well not have pursued it. When we received the grant, we felt we were, collectively, under his nurturing influence.

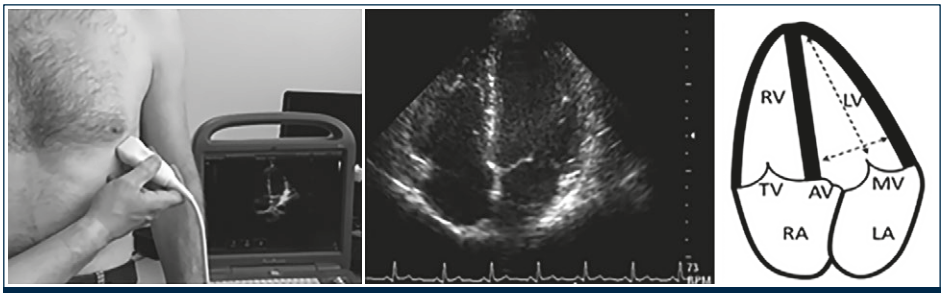

Figure 1. **A4C – what's happenin'... to the left ventricle during exercise!** The apical four chamber (A4C) view is one of the most intuitive cardiac images that can be obtained by ultrasound. Measurements of ventricle length and diameter in this view allows estimation of left ventricular volumes during diastole and systole. Hence, end diastolic diameter (or stretch) and stroke volume can be calculated before and immediately after exercise, then discussed in the context of the Frank–Starling law of the heart. Clinical measurement involves slightly different procedures that have been adapted for teaching purposes.

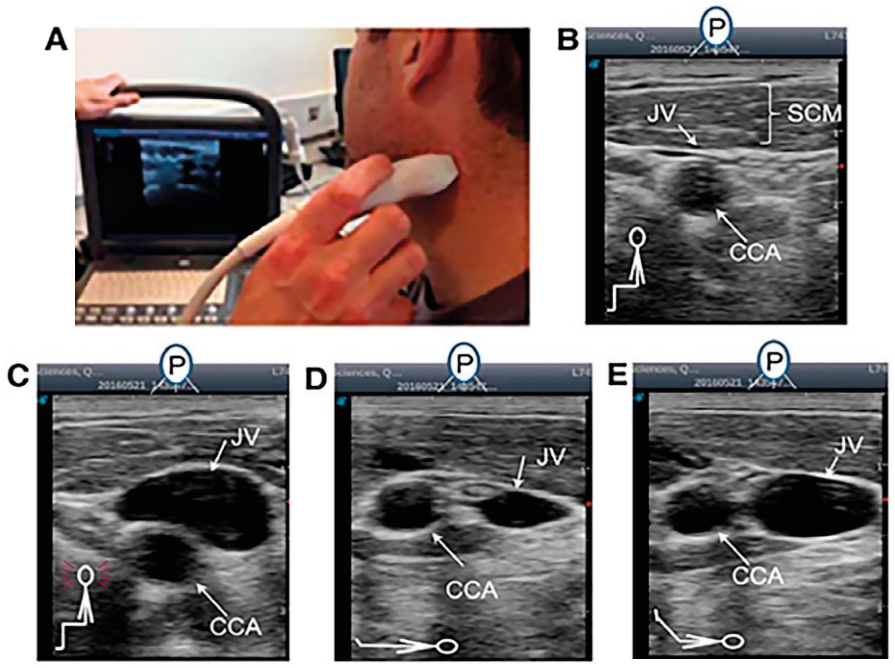

Figure 2. **Jugular vein and CVP.** Transverse section through the neck approximately 10 cm above the clavicle in an upright subject, showing a cross section through common carotid artery (CCA) and internal jugular vein (JV) (A). The sternocleidomastoid muscle (SCM) is visible, between the vein and the ultrasound probe (P). The jugular vein is relatively collapsed at this level. In this same position, JV inflates somewhat like a balloon when the subject increases intrathoracic pressure by procedures such as the Valsalva manoeuvre (B). When the subject lies flat, the relative increase in JV pressure allows JV to inflate and is easily visible (C). This increased pressure is exacerbated by raising the legs by 60 cm (D). If the ultrasound probe is allowed to take a transverse section of the neck 2-3 cm below the angle of the jaw, then JV and CCA (before bifurcation) are easily visible (E). The inset 'stick men' indicate body position, which may be discussed in relation to changes in venous return to the heart.

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