PN
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News

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Medical Technology Special Issue:

Leveraging Physiology in Patient Care

The Physiological Society

Physiology News

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Welcome to the Spring 2021 edition of *Physiology News*

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Cover image: The Iron Lung ward at Rancho Los Amigos Hospital, c. 1953. From: http://www.fda.gov/cber/summaries/cent092302pp.htm

Physiology on the frontline

Julia Turan
Managing Editor, *Physiology News*

Keith Siew
Scientific Editor, *Physiology News*

"This issue has been more challenging than most to assemble, as colleagues were redeployed to rapidly filling wards or scrambling to restructure their teaching at a moment's notice"

Little did we know, when we chose to dedicate an issue to this theme back in early January 2020, that it would land at a time so *apropos*. Now, as we sit here writing this editorial, over a year later and approaching the end of our third national lockdown, we must admit that this issue has been more challenging than most to assemble, as colleagues were redeployed to rapidly filling wards or scrambling to restructure their teaching at a moment's notice. So, it is with sincerest thanks to our contributors and great excitement that we welcome our readers to this Special Issue of *Physiology News* focusing on the interplay between physiology and medical technology in patient care (something of which we are all more acutely aware of late).

Today, with the plethora of devices beeping, humming and buzzing about a modern hospital ward, it is perhaps easy to forget that the practice of extending our senses to explore physiological phenomena is centuries old. Some of the earliest of these devices can be dated back to the beginning of the 17th century, at a time when a patient's pulse rate was calculated not by time but length using a pulsilogium. Invented in 1602 by Santorio Santorio, the pulsilogium took advantage of his friend's insight (incidentally Galileo Galilei) into the frequency of a pendulum's oscillation being inversely proportional to the square root of its length. And so, by synchronising the swing of a pendulum to a patient's pulse through adjustment of the cord length as measured against a ruler, heart rate could be accurately determined for the first time (Fig. 1, left). In 1612 he went on to describe the thermoscope, another creation by his friend Galileo that he repurposed for medical usage. Composed of an air-filled glass ball attached to a long, thin graduated glass pipe submerged in a reservoir of water (Fig. 1, right), he could measure (semi-quantitative) changes in a patient's temperature as a column of water moved up/down the glass pipe upon placement of the glass ball in either the hand or mouth. These, combined with his "weighing chair" invention, were the first truly quantitative tools for physiological experiments and his pioneering of their clinical usage forever changed patient assessment.

The next advancement in assessing the heart would come with the invention of the stethoscope in 1816 by René Laennec, which came about not through rigorous scientific endeavours but rather because of embarrassment at the seeming impropriety of putting his ear to the chest of a young female patient. Serendipitously, he discovered that a rolled-up tube of paper (later refined into a wooden tube) could augment the auscultation of heart sounds (Fig. 2). Following in the trend of non-invasive measurements, the sphygmograph – a system of levers and weights used to stop blood flow in the radial artery – was developed in 1854 by Karl von Vierordt to estimate blood pressure, and later modified to record pulse waves (Fig. 3). These early innovations have paved the way for their 21st century digital descendants, and during this period of social distancing, heart-monitoring smartwatches have been used to detect life-threatening episodes of atrial fibrillation in outpatients (p. 14).

It is also easy to forget that the practice of medicine is not confined to bipedal hominids, but also extends to our furry companions and the progress made in veterinary care and animal experimentation often precedes human care (p. 10). None better encapsulates this than Augustus

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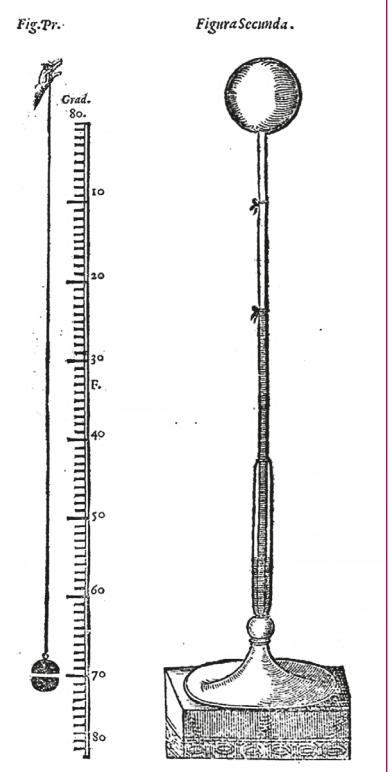

Figure 1. Illustrations from *Commentaria in primam Fen primi libri Canonis Avicennae* by Santorio Santorio, 1626. (Left) Pulsilogium - used to measure heart and respiration rates in an objective, quantitative and repeatable way for the first time. (Right) Thermoscope - used to record the first non-invasive body temperatures via placement of the bulb in the mouth or hand. [© Wellcome Collection. Source: bit.ly/2OdSqoN. Licenced under CC BY 4.0].

Figure 2. One of the first wooden stethoscopes made for auscultation of heart sounds (c.1820). The label reads: "*This is one of Laennec's original stethoscopes, and it was presented by him to Dr Bégin, a French Army surgeon whose widow gave it to me in 1863.*" [© The Board of Trustees of the Science Museum. Source: bit.ly/3tbCsKE. Licenced under CC BY 4.0]

Desiré Waller who toured the lecture circuit with his dog Jimmy, demonstrating the utility of his recently (c.1887) invented electrocardiogram. In 1913, Abel, Rowntree and Turner demonstrated the first use of an "artificial kidney" in living animals, an essential milestone in the development of the modern dialysis devices keeping millions alive today (p. 26). And in a more modern example, Hagisawa *et al.* (p. 22) have shown the utility of their novel artificial blood products in haemorrhagic emergencies in the veterinary setting, and have now commenced their first clinical trials for human use.

However, perhaps the best example of the convergence of medical technologies and physiology have centred around this pandemic. Indeed, many physiologists have and continue to play significant roles in the COVID-19 response. In particular, the work of the Doyle group (p. 19), who specialise in the treatment of thrombi, will be of increasing importance in understanding the pathophysiology of COVID-induced thromboembolism (with overall rates of venous thrombosis averaging 21% among non-ICU hospitalised patients). The issue also includes perfusionists sharing their experiences of providing ECMO life support to the most critical patients (p. 38), and an account of the redeployment of physiologists ranging from audiology, neurophysiology and gastrointestinal physiology to support critical care teams and patients (p. 40).

And we hope you too are as amazed as us by the work of our clinical physiologist colleagues.

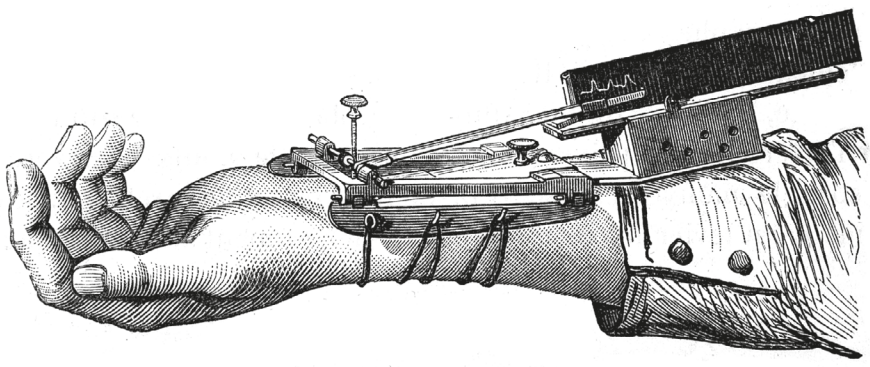

Fig. 109. Sphygmographe direct.

Figure 3. The sphygmograph was used to non-invasively measure blood pressure in the mid-19th century. This illustration from *La circulation du sang à l'état physiologique et dans les maladies* by Etienne-Jules Marey, 1881, shows the improved portable design which could magnify and record pulse waves on paper. [© Wellcome Collection. Source: bit.ly/2N9hnkF. Licenced under CC BY 4.0]

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Turning a new leaf, whilst honouring our past

David Paterson

President, The Physiological Society

A Happy New Year to all of you in these challenging times. This is my first "President's View" message. I am delighted to have the honour of acting as your spokesperson for the next 2 years. For those of you who do not know me, my day job is Professor of Physiology and Head of the Department of Physiology, Anatomy & Genetics at the University of Oxford, and a Fellow of Merton College, Oxford, UK. As a research-led teaching academic I lecture medical and biomedical sciences students and run a British Heart Foundation (BHF)-funded research group, which is concerned with the neurobiology of cardiac excitability in pathophysiological states. I have been a long-standing member of The Society and was recently Editor-in-Chief of *The Journal of Physiology*, and prior to that, Editor-in-Chief of *Experimental Physiology*. In 2018 I co-authored the textbook with Neil Herring, *Levick: Introduction to Cardiovascular Physiology* (6th edition).

It is important that I use this opportunity to thank Professor Bridget Lumb for her excellent service to The Society over the last 2 years. The Society has accomplished so much under her outstanding leadership, driving The Society forward to be more inclusive and diverse. A key part of achieving this was completing the Governance Review, ensuring that The Society has strong foundations on which to build. Bridget has also championed work in policy that has raised the profile of the discipline with key stakeholders. Her legacy is secured as first female president of The Society, which she has left in very good shape.

I would also like to congratulate all those elected as Trustees at the Member Forum in November 2020: Professor David Attwell as President-Elect, Dr Lucy Green as Chair of Education, Public Engagement and Policy Committee and Dr Daniel Brayson as Early Career Trustee.

I am also pleased to report that in December, Trustees agreed to appoint Professor Paul McLoughlin to Chair of Publications Committee and Dr Catherine Hall to Chair of Conferences Committee. Both members will be taking up their positions at the Member Forum in November 2021 but will shadow the current chair until then.

I believe that physiology faces challenges, but these give rise to opportunities. Particularly important over the last 25 years has been the decline of physiology departments over the UK and the US with physiology often being perceived as a phenotyping tool for the genomics community. Of course, physiology is more than this; it is primarily a discovery science, and is at the core of the medical curriculum with research-led education given to healthcare professionals. At least 58 of The Society's members have been awarded the Nobel Prize for Physiology or Medicine, from Ivan Pavlov (1905) to Sir Peter Ratcliffe (2019).

The COVID-19 pandemic is certainly going to shape all of our lives, but equally it should not define us. This multi-organ disease has highlighted the unique role that physiology plays in understanding how organ systems communicate in pathophysiological states, and alongside other such areas that The Society is working in, such as understanding why "exercise is medicine" and the ageing process, will place physiology at the fore again. Readers of *Physiology News* do not need convincing of the importance of our science legacy, but they do need a clear narrative about where we are now and our future.

The phrase that I would like to define my presidency by is: "enhancing the visibility of both the subject area and The Society".

As a membership organisation we would like to hear what our members have to say about COVID-19 and other topics relevant to physiology and The Society. COVID-willing we will be visiting institutions around the UK and Ireland during the next 2 years. The roadshows should also encourage wider interaction by bringing members and non-members, who have an interest in physiology, together to provide a forum where they can network locally and gain access to new communities.

We need to build our membership both by re-engaging with our core base while reaching out and appealing to new members. We want to be an inclusive and diverse membership and I am fully supportive and enthusiastic about The Society's newly formed Equality, Diversity, and Inclusion (EDI) Task Force that will be developing a programme of activity and EDI strategy for Trustees to review.

Whilst moving The Society forward is key to maintaining relevance, it is important to acknowledge our heritage and to build on this distinguished past. One of the initiatives that we will be rolling out in 2021 is a Society blue plaque scheme. The aim of the scheme is to celebrate and recognise institutions where pioneering physiologists such as Nobel Laureates and our first women physiologists have made their significant contributions to the discipline. This is part of the wider strategy to raise the profile of the discipline both with the public and with physiologists, increasing the prestige associated with physiology at university departments and highlighting the legacy of physiology academia to potential students.

There is a lot to do, but I hope you will all join me in making sure that the value of physiology is fully valued and continues to thrive. We are all keen to meet again in person. As confidence grows with the vaccine roll-out, the future will be bright again.

Read David Paterson's article "The real value of research" in the last edition of The Foundation for Science and Technology Journal: ***foundation.org.uk/Journal***

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An exciting year ahead of strengthening our community and networking opportunities

Dariel Burdass

CEO, The Physiological Society

One of the most important elements of a learned society is its membership, and members are at the heart of The Society's strategy. For 2021 we have launched a contemporary and inclusive new suite of membership categories. This will better support our members, both those in academic and non-academic physiology-focused careers. These changes will enable us to further tailor member benefits for each career stage and to increase the breadth of our membership.

To enable members to continue to network and share scientific knowledge, and to strengthen our membership benefits, we will be continuing to offer a wide range of webinars in 2021. In 2020, we ran three successful professional development (PD) webinar programmes. The longest-running series took place during the first lockdown and was designed specifically for members. The webinars were well attended, particularly by our early career physiologists, and received positive feedback including some suggestions for future sessions.

We intend to build on this success with three further programmes running in 2021; the first will run in March and will support undergraduates. There will be two subsequent series: one for postgraduates and one for academics looking to progress their career through teaching and learning in higher education.

Building on the success of our Scientific Theme webinars, it is our intention to run two of these webinars per month in 2021 and the call remains open for members to submit their proposals. We have three in the pipeline so far. Our PD webinars and Scientific Theme webinars are free for members to attend with access to the recording after the event. Non-members will need to pay £20 to watch live with a 7-day catch up.

During 2021 we will also be launching a new grants programme, for funding opportunities in 2022 and onwards, which is designed to achieve a coherent programme of end-to-end support for our members. The goal of the programme is to both encourage and reward long-term membership, but also to develop a cadre of advocates for physiology and The Society. Further details to follow.

Under construction on our website is a new member area with resources and activities that are exclusive to members. This member area, along with our growing programme of member-only content, is part of our ongoing investment in the future of physiology.

To enable us to successfully deliver our programme of activities we rely on our loyal and engaged membership, which we are looking to broaden and grow. If you know of someone who is a lapsed member or is a potential member let them know about our new membership categories, which can be found on our website.

In addition, we will shortly be opening our nominations for the next round of Board appointments; we will be looking to appoint three General Trustees to take up office at the 2021 November Member Forum. Being a Trustee is a critical role within The Society and if you would like to influence our future direction, I would encourage you to apply. Further details will be posted on the website and members will be notified through our newsletter.

Our membership is a unique source of expertise and knowledge and we are fortunate to be able to harness this to inform our policy work. The Society has already begun to have more influence shaping UK policy in areas of physiological concern such as ageing, obesity and exercise.

The risks of serious illness from COVID-19 requiring hospitalisation and dying both rise with age; consequently, in November 2020 we launched our report, *A National COVID-19 Resilience Programme: Improving the health and wellbeing of older people during the pandemic*. This project brought together physiologists, nutritionists, geriatricians, physiotherapists, and clinicians to discuss the physiological factors behind why the risk of COVID-19 disease severity rises with age. The project was a collaboration between The Society and Centre for Ageing Better, part of the UK Government's What Works Network and the report was launched at the Discussion Meeting of the UK Parliamentary & Scientific Committee.

We highlighted the physiological evidence demonstrating that physical activity (with tailored exercise or physical activity goals) represents one of most impactful ways in which older people can reduce the risk of developing severe COVID-19, improve recovery, and limit deconditioning and frailty from home confinement. We recommended that the Government introduce a National COVID-19 Resilience Programme to bring together a package of measures to support older people through the lockdown and beyond, keeping them healthy and resilient over the winter.

The report was covered in national media and we have subsequently engaged with a variety of key stakeholders, such as the NHS, Public Health England, local authorities, and the Chief Medical Officers.

In January of this year, the House of Lords Science and Technology Select Committee released its inquiry into Ageing entitled *Ageing: Science, Technology and Healthy Living*. I am delighted to report that there is significant inclusion of material from our *Growing Older Report* in this inquiry with The Society being recognised and Society members contributing.

Also, in January, we launched our latest report, *Translating UK knowledge and research into impact: Physiology and Knowledge Exchange*. The report can be downloaded from our website: **physoc.org/knowledge-exchange**

The launch event participants heard from the Executive Director of BBSRC, Melanie Welham, and we also showcased how physiology knowledge and research is translated into impact.

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.

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.

Fellow membership recognises the experience and contributions of our distinguished members. Apply by 1 May to become a Fellow Member **physoc.org/fellow**

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Ensuring a funding environment that reflects the impact of physiology

Tom Addison

Policy Manager,
The Physiological Society

The recent announcement of a review of the Research Excellence Framework (REF), implementation of the Knowledge Exchange Framework (KEF) and the UK Government commitments to increase UK science funding mean that research funding is under unprecedented scrutiny by the UK Government and funding organisations. To ensure a healthy funding landscape for physiology, The Society has been working with policymakers, industry, UKRI and higher education institutions to champion the benefits physiological research brings the economy and wider society.

Firstly, towards the end of January, The Society launched its joint report with the National Centre for Universities and Business (NCUB) *Translating Knowledge and Research into Impact*: *Physiology and knowledge exchange*. This project's Advisory Group was co-chaired by members Professor Tim Curtis from Queen's University Belfast and Dr Richard Siow from King's College London and included participation from representatives of AstraZeneca, GlaxoSmithKline and PraxisAuril. Knowledge exchange, as the report notes, describes the multiple interactions between higher education institutions and businesses, public services, charities, the public, policymakers and Government that create societal and economic benefit and account for about £5 billion of the UK's academic sector.

While universities are required to declare their knowledge exchange income and break it down roughly into different academic sectors (bioscience, law, humanities etc.), a comprehensive discipline-specific approach to analysing these data has never been undertaken.

In doing so, The Society will give funders and policymakers a better idea of the type of financial and social contribution that physiology makes and also demonstrate the breadth of physiological research's impact. For example, one knowledge exchange team found that physiological research conducted at their institution had been cited as evidence in a legal case.

Additionally, the report seeks to better understand the types of knowledge exchange that physiologists undertake and why. For many years, the prevailing view among some was that knowledge exchange only meant commercialisation and licensing and that was only undertaken for an individual researcher's financial benefit. In truth, our report found that commercialisation of research makes up a small proportion of overall physiological knowledge exchange (about 7% of the universities that provided data) and seeking one's own fortune ranked as the least popular driver of knowledge exchange activity (about 13%). Physiologists were more likely to use knowledge exchange as an opportunity to inspire new research (55%), to translate their research into a benefit (42%) or to further their institution's outreach mission (42%). Knowledge exchange then, is not just about the money but the financial data help us to make an evidenced-based argument for the return on investment of public funds.

> "To ensure a healthy funding landscape for physiology, The Society has been working … to champion the benefits physiological research brings the economy and wider society."

This report includes input from over 250 stakeholders from across physiology: university knowledge exchange teams, industry partners and organisations that support collaboration between them. The report launch reflected this, with opening remarks from the Chief Executive Officer of BBSRC, Professor Melanie Welham, as well as remarks from some of our Advisory Group members from organisations such as NCUB, GlaxoSmithKline and King's College London. To read the report and watch the recording of the launch event, please visit **physoc.org/knowledge-exchange**.

Secondly, The Society held a joint roundtable workshop with the Campaign for Science & Engineering (CaSE) on barriers to greater interdisciplinary funding and working along with senior management from universities and other learned societies and membership organisations. This wide-ranging discussion touched on several recommendations that The Society outlined in *Growing Older, Better,* particularly on the challenges of writing grant applications that appeal to the expertise of multiple funding panels. A summary report from the session can be downloaded from **physoc.org/interdisciplinary**

A final example of one of the ways The Society's policy work has impact is the Lords Science and Technology Committee's long-awaited report into the UK Government's approach to meeting the challenges of an ageing society, *Ageing: Science, Technology and Healthy Living*. In places, the Lords report quotes directly from The Society's 2019 report *Growing Older, Better* around the need for greater urgency in reaching the Government's Ageing Society Grand Challenge of an average increase of "five healthier, more independent years of life by 2035"[1] and the need to underpin this ambition with a better understanding of the mechanisms of ageing and age-related diseases.

As the activities described above outline, The Physiological Society will continue to look for opportunities to make the case for improved funding processes for physiology. The publication of *Translating Knowledge and Research into Impact* is timely given the introduction of the KEF this year and with the announcement that the REF criteria will be reviewed after this year's cycle, there is again an opportunity to make the case for a greater focus on interdisciplinary research such as physiology.

In the meantime, there is an opportunity to read the report at **physoc.org/knowledge-exchange** and share the report with your colleagues.

References

1. https://www.ukri.org/wp-content/uploads/2020/11/UKRI-131120-SocialInvestmentReport-V2.pdf

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Leading award recognises The Society's support for members during COVID-19

The Physiological Society has won an industry-leading award, from The Association of Association Executives, for the support we offered members during the COVID-19 pandemic.

The Association of Association Executives is composed of 23,000 membership organisations and subscribers from across the world. At their annual UK award ceremony this past December, The Society beat tough competition to win the category called Best Member Support during COVID-19.

In March 2020 as the UK went into its first national lockdown, The Society launched its COVID-19 Hub. This Hub continues to provide links to a range of activities that support members on a professional and personal level, as well as providing a virtual community that continues to evolve, including:

- Free professional development webinars for members
- A series of member-focused scientific webinars to facilitate online conversations with like-minded physiologists
- A virtual journal club to enable physiologists to meet on a regular basis to discuss papers that have been published in *The Journal of Physiology*
- Support and guidance on returning to the laboratory safely
- Aid to members in the most difficult of financial situations, including those resulting from COVID-19
- Mental health resources, including online training courses and guidance on providing a supportive environment for the management of stress
- All research papers related to COVID-19 published in *The Journal of Physiology* and *Experimental Physiology* are free to access.

The Society also convened a COVID-19 Advisory Panel last year to bring physiologists and clinicians together to provide an evolving understanding of the physiological and pathophysiological mechanisms underpinning this disease.

The online meetings organised as part of the COVID-19 Hub have been extremely successful, with over 650 physiologists sharing advice on returning to the lab safely, resulting in the production of guidance documents for our community.

Throughout the challenging and unfamiliar past year of the pandemic, The Society has adapted our activities and resources to support our members and the academic community. This was only possible because of the innovative, responsive, and collaborative way that Society members, Trustees and staff came together to pool resources and new ideas.

Building on the COVID-19 Hub, this year we will be launching a new member area and online community. As it is clear that we will be living with the impact of COVID-19 for some time, The Society is determined to continue supporting our members both now and in the future.

The Board of Trustees – September 2020

The Board met virtually on 17 September 2020. The Honorary Treasurer informed the Board of Trustees that in financial terms COVID-19 had made a positive financial impact on The Society with cancelled and delayed expenditures leading to a surplus. The Board reviewed the Risk Register and the Honorary Treasurer highlighted dependency on a single source of income as the continuing highest risk to The Society.

The Board agreed to support the 2020 meeting of the Latin America Association of Physiological Sciences, 16 – 20 November 2020.

The Chair of Publications Committee and the Director of Scientific Programmes introduced a paper on open access and direction of travel. Trustees agreed on the importance of remaining agile and informed as Plan S continues to evolve.

Trustees discussed the upcoming virtual conference – COVID-19: Lessons Learned from the Frontline – which The Society is hosting with the Intensive Care Society, 14 – 16 December 2020. It was noted that the conference would bring together physiologists and clinicians with the programme covering the different systems and organs that have been affected by COVID-19.

The Chair of Conferences Committee and the Director of Scientific Programmes presented a paper to the Board on the options analysis for our annual conference Physiology 2021. Trustees discussed the options and agreed that, if possible, the conference should be hosted as a hybrid event.

On behalf of the Board, the President-Elect thanked the President for her stewardship, leadership, and the tremendous amount of work she had put into the governance review of The Society. He noted that the President had been a great ambassador not just for The Society but for the subject itself.

The President thanked the President-Elect for his kind words and noted that she had enjoyed her time as President very much. She added that much had been achieved and that she had greatly enjoyed working with both the staff and with fellow Trustees.

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Ventilating the furry ICU patient

A veterinary perspective on mechanical ventilation in the ICU

Helen Wilson

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Modern mechanical ventilators are a far cry from their "iron lung" predecessors and yet, in this COVID-19 pandemic, we have intensive care units filled with rows of patients on ventilators, just as we did in the 1950s, with rows of poliomyelitis patients confined to the metal cylinders that were their only means of breath. The COVID-19 pandemic has put the indispensable mechanical ventilator firmly into the public arena once more.

Modern permutations of ventilators are highly complex pieces of equipment capable of monitoring tidal volumes and airway pressures, as well as responding to patient respiratory efforts. They even come complete with disco-esque flashing lights and musical alarms (which I often hear in my sleep). Mechanical ventilation is employed not only for humans, but also to help our furry companions breathe more easily, which came full-circle last year when the ventilators from our veterinary hospitals were re-deployed to human hospitals to help meet the demand at the start of the pandemic.

Poliomyelitis epidemics were frequent throughout the first half of the 20th century, with 1 in 200 victims suffering respiratory paralysis and requiring ventilatory support via an iron lung. Patients often had secondary pneumonia and survival rates were poor, around 15 – 20% (Woollam, 1976).

The iron lung worked on the principle of negative pressure ventilation. It was essentially a sealed chamber containing the patient's body, with only their head protruding. A pump generated a sub-atmospheric pressure within the chamber, which consequently expanded the patient's rib cage, thus increasing the intrathoracic volume and in turn generating negative pressure within the thoracic cavity, to draw air into the lungs through the nose and mouth.

In Copenhagen in 1952, Drs Henry Lassen and Bjørn Ibsen developed the technique of providing manual intermittent positive pressure ventilation through a high tracheostomy for poliomyelitis patients, and saw a dramatic reduction in their mortality figures from 80% to 40% (Woollam, 1976). Cue the era of the modern mechanical ventilator.

Despite the better success rates of positive pressure ventilation, there are a number of physiological advantages of negative pressure ventilation. A normal physiological inspiration is a negative-pressure event, generated by the contraction of the external intercostal muscles and the diaphragm, expanding the thoracic cavity and reducing the intrathoracic pressure, thus drawing air into the lungs, in exactly the same way as the iron lung. A positive pressure breath is essentially the opposite of a physiological breath. Air is forced into the lungs at supra-atmospheric pressure, to forcibly expand the pulmonary parenchyma. With both types of ventilation, expiration is passive, relying on the elastic recoil of the chest as in

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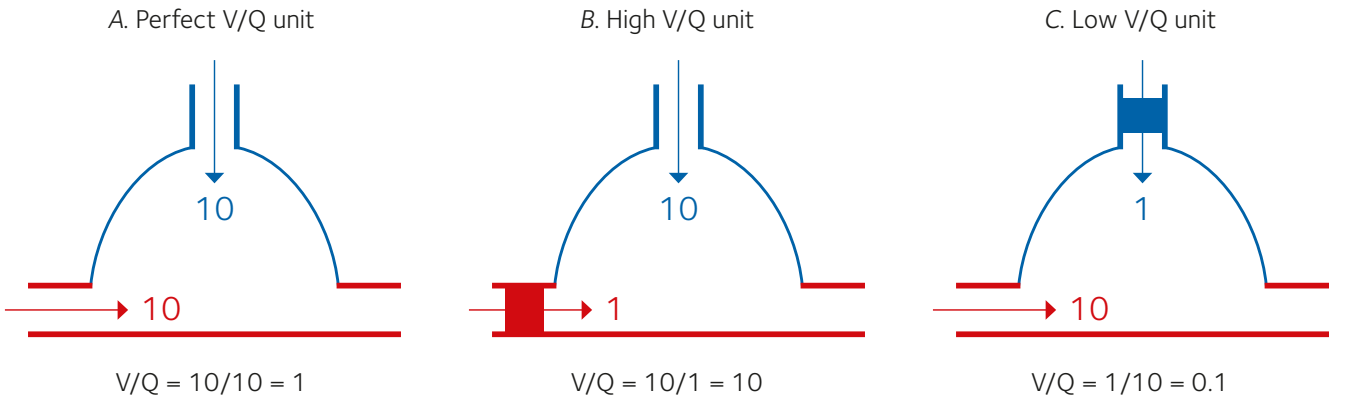

Figure 1. Schematic representation of V/Q units. *A.* shows perfect matching of ventilation with perfusion, giving a V/Q ratio of 1. *B.* shows a high V/Q unit, with a V/Q ratio of greater than 1, occurring when perfusion is reduced. *C.* shows a low V/Q unit, with a V/Q ratio of less than 1, occurring when ventilation is reduced.

normal resting expiration. Intuitively, it makes sense to use negative pressure over positive pressure ventilation for its greater alignment with normal physiology, but both modalities have limitations. Modern medicine focuses on positive pressure ventilation, due to its superior control over pulmonary dynamics and advantages for ventilating diseased lungs.

Initiating positive pressure ventilation in dogs and cats

The aim of mechanical ventilation is to maintain normal oxygenation and ventilation, with the least aggressive ventilator settings. In veterinary critical care, there are three criteria for initiating mechanical ventilation, of which a patient need fulfil only one (Vassilev and McMichael, 2004). First, severe refractory hypoxaemia; second, severe hypoventilation; and third, excessive work of breathing with impending respiratory fatigue or failure. Hypoxaemia is defined as partial pressure of arterial oxygen (P_aO_2) < 80 mmHg and hypoventilation as partial pressure of arterial carbon dioxide (P_aCO_2) > 45 mmHg. In veterinary medicine we use the 60/60 rule for determining the need for mechanical ventilation. If the P_aO_2 is < 60 mmHg, or the percutaneous oxygen saturation (S_pO_2) is < 90% as an equivalent marker of oxygenation, despite oxygen therapy, or if the P_aCO_2 is > 60 mmHg despite treatment, then mechanical ventilation is indicated. The third criterion is a clinical decision and allows for the institution of mechanical ventilation if a patient's welfare is severely compromised by their dyspnoea.

There are five causes of hypoxaemia (West, 2008):

1. Hypoventilation
2. Ventilation–perfusion (V/Q) mismatch
3. Right-to-left shunt
4. Diffusion impairment
5. Reduced oxygen tension in inspired air (P_iO_2), i.e. hypobaric or inspiratory hypoxia

Total oxygen content in the blood is further affected by anaemia and aberrant haemoglobin species, but these patients will have a normal P_aO_2 and therefore will not benefit from mechanical ventilation; rather they require restoration of their haemoglobin levels to improve their tissue oxygenation.

Hypoventilation results in reduced minute volume and inadequate elimination of CO_2 from the lungs, hence these patients develop hypercarbia (i.e. increased blood CO_2). Hypoventilation is always associated with hypoxaemia, due to a failure of fresh gas delivery to the alveoli, but the hypoxaemia is readily reversed with oxygen supplementation, while the P_aCO_2 remains unchanged without mechanical ventilation.

Ventilation–perfusion (V/Q) mismatch and shunt are a continuum of disease severity and are the most common reasons for hypoxaemia to occur in veterinary medicine. For oxygen to diffuse into the blood and for carbon dioxide to diffuse out of the blood, there must be even matching of the alveoli that are being ventilated (receiving air) and those that are being perfused. If ventilation and perfusion were perfectly matched across the lungs, the V/Q ratio would be 1 (Fig. 1A).

V/Q matching is not perfect in healthy lungs, resulting in a V/Q ratio of 0.8 averaged across the whole lung, because of the effect of gravity on the distribution of perfusion from the top to the bottom of the lungs and the effect of the weight of the lungs on ventilation. that which are being ventilated but inadequately perfused are called high V/Q units (Fig. 1B) and those being perfused but inadequately ventilated are low V/Q units (Fig. 1C).

Zero V/Q units are alveoli that are being perfused but receiving no ventilation and this indicates alveolar collapse or small airway obstruction. Zero V/Q units give rise to a right-to-left pulmonary shunt, which is a region of lung that is perfused but not ventilated, resulting in blood entering the left side of the heart that has traversed the lungs without picking up any oxygen. This volume of blood is called the shunt fraction.

Hypoxaemia due to zero V/Q units or whole regions of diseased lung resulting in shunt will not respond to oxygen supplementation and requires positive pressure ventilation to open up these collapsed alveoli. It is unlikely that negative pressure ventilation would be helpful for such severely compromised regions of lung. We often perform so-called recruitment manoeuvres on ventilator patients to transiently increase the pressure within the airways and open up collapsed regions of alveoli in severely diseased lungs, thus improving V/Q matching.

Diffusion impairment results in hypoxaemia through thickening of the barrier between the alveolar and capillary lumens. This can occur in pulmonary fibrosis, which can develop secondary to severe inflammatory diseases such as acute respiratory distress syndrome (ARDS). ARDS can result from many diseases, including SARS-CoV-2 infection (COVID-19) and it remains to be seen if people who have recovered from COVID-19 will go on to develop pulmonary fibrosis and longer-term hypoxaemia. Because carbon dioxide has greater solubility than oxygen, it diffuses 20 times faster, meaning that hypercarbia is rarely due to diffusion impairment, whereas hypoxaemia can be.

Finally, hypoxaemia can be due to reduced fraction of inspired oxygen (F_iO_2), typically due to equipment failure when animals are intubated and connected to a breathing circuit.

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"Patients requiring ventilation fall into one of two groups – those with healthy lungs and those with diseased lungs"

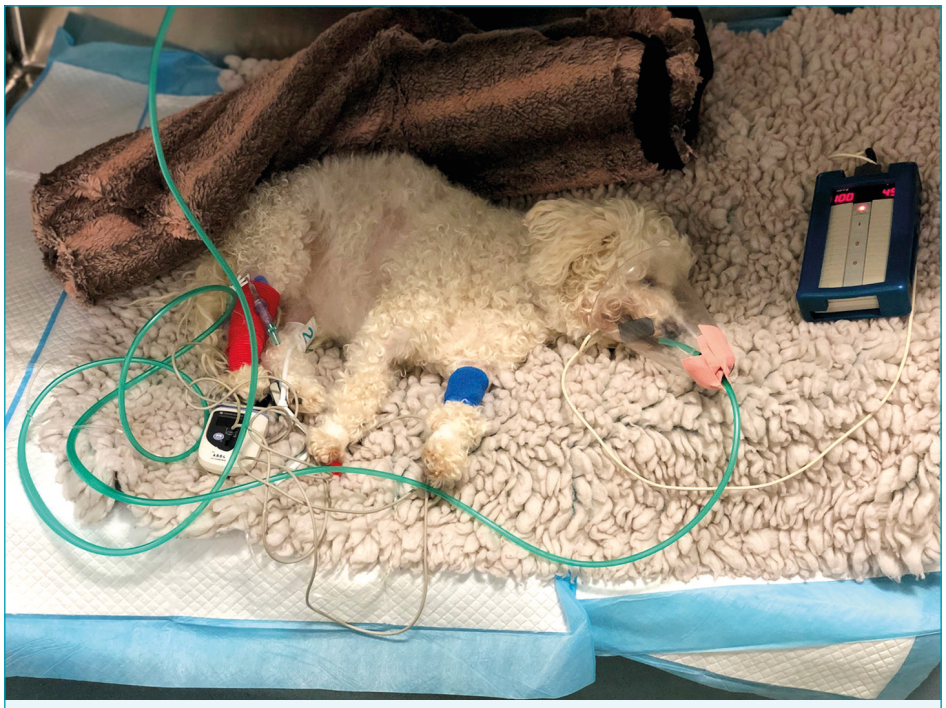

Figure 2. Pulse oximetry using the buccal mucosal membrane of an obtunded, critically ill dog.

Assessing ventilation and oxygenation in animals

Hypoventilation can be easily assessed on a venous blood gas sample, due to the consistent difference of 3 – 6 mmHg between arterial and venous PCO_2 in animals (Lumb, 2017). Conversely, assessing oxygenation can be challenging in veterinary medicine. Minimal handling is important for dyspnoeic patients, particularly cats, as they are prone to cardiopulmonary arrest when stressed. This can make obtaining an arterial blood gas challenging. Pulse oximetry can provide us with a surrogate marker of oxygenation but is also fraught with difficulty. Sadly, we cannot ask our patients to sit still while we put a probe on their finger. Our patients' fur also interferes with pulse oximetry readings. The most reliable place to obtain a pulse oximeter reading from is the tongue, which is only feasible when the patient is under anaesthesia if you value your fingers and the probe. The buccal mucosal membrane is the best place to obtain a reading from in a conscious patient (Fig. 2) but is frequently pigmented in animals and often poorly tolerated, resulting in unreliable readings. Alternative mucous membranes that can be helpful include the prepuce and vulva and less-furry areas that may be fruitful include the inguinal region, ears and digits.

The problem of oxygen toxicity

Interestingly, oxygen itself can be toxic and veterinary species are more susceptible than humans (Lumb, 2017). Oxygen is a free radical, possessing two unpaired electrons. This makes it and some of its derivatives highly reactive, with a tendency to steal electrons from other molecules. Fatty acids in membrane phospholipids are particularly rich in readily available electrons and therefore highly prone to oxidative damage. Free radical oxidative damage to cell membranes triggers apoptosis and inflammation. In the lung, this can lead to hyaline membrane formation and progressive fibrotic change, with histological changes indistinguishable from those associated with ARDS. The toxic threshold is an F_IO_2 of 50% for 24 hours or more (Fisher *et al.*, 1984). For this reason, we always aim to reduce the F_IO_2 to below this threshold within the first 24 hours of mechanical ventilation, although this is sometimes not possible due to disease severity.

Ventilating healthy vs. diseased lungs

Patients requiring ventilation fall into one of two groups – those with healthy lungs and those with diseased lungs. Patients with healthy lungs requiring mechanical ventilation are those with neurological diseases causing hypoventilation. Negative pressure ventilation may be effective for patients with healthy lungs but is less likely to work adequately for patients with diseased lungs, particularly those with severe disease and regions of zero V/Q units and shunt. These patients require the application of positive pressure breaths to open up and recruit the collapsed regions of lung to alleviate their hypoxaemia (Brower *et al.*, 2000), thus explaining the mortality benefit over negative pressure ventilation discovered by Drs Lassen and Ibsen in poliomyelitis patients, who frequently had secondary pneumonia.

However, all pulmonary diseases in dogs and cats can result in reduced compliance, meaning that the lungs are stiffer and expand by a smaller volume for any given increase in pressure compared with healthy lungs. Positive pressure can damage the lung, both by excessive pressure (barotrauma) and by excessive volume (volutrauma). Together, these sequelae of positive pressure ventilation are called ventilator-induced lung injury (VILI). VILI can lead to worsening inflammation of the lungs, worsening compliance and even pneumothorax. The risk of VILI is increased as pulmonary compliance worsens and VILI is associated with an increased risk of death in ARDS (Brower *et al.*, 2000). Interestingly, in 1951, Plum and Lukas noted an association in negative pressure ventilation between larger tidal volumes and the development of pulmonary emphysema, implying that excessive negative pressure can also cause a form of VILI.

The importance of prone positioning in ventilated people was recognised as early as 1952 and was a problem of negative pressure ventilators, which did not allow for this (Woollam, 1976). Prone positioning has been shown to reduce mortality in humans with ARDS undergoing positive pressure ventilation (Sud *et al.*, 2014) and recently has been shown to avert 1 in-hospital death for every 8 patients ventilated with ARDS due to COVID-19 (Shelhamer *et al.*, 2020). This is because in the prone position, the volume of lung that is collapsed under its own weight is reduced compared with the supine position, thus improving V/Q matching. Dogs and cats are naturally in the prone position during mechanical ventilation, offering us an advantage compared with our human counterparts (Fig. 3).

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Newer respiratory support technologies in the veterinary ICU

The rise of less invasive technologies such as continuous positive airway pressure (CPAP) and high-flow oxygen have helped to reduce the number of patients that require mechanical ventilation and the associated morbidities. When delivered via a mask, CPAP is not well tolerated by veterinary patients without heavy sedation, as animals dislike having a mask over their face and the long noses of dogs do not fit the masks well. Therefore, CPAP can only effectively be delivered to animals via a helmet (Ceccherini *et al.*, 2020) or to intubated patients. There are a number of limitations to helmet ventilation and, consequently, we most commonly use CPAP as a means of weaning patients from mechanical ventilation, rather than a way of negating it. On the other hand, high-flow oxygen is proving extremely useful in the veterinary ICU. High-flow oxygen is warmed, humidified oxygen, which can be delivered through nasal prongs at significantly higher flow rates than traditional oxygen therapy, therefore dramatically improving P_aO_2 (Jagodich *et al.*, 2020). The humidification means it is much better tolerated and less likely to cause desiccation of the nasal turbinates (the mucosal surfaces within the nasal cavity), which leads to patient discomfort and the risk of rhinitis from secondary infection. In addition, the delivery of high-flow oxygen requires fewer resources and less expertise than mechanical ventilation, making it significantly cheaper. In the veterinary sector, high-flow oxygen is revolutionising our care of dogs with severe hypoxaemia, which would otherwise have required mechanical ventilation. Sadly, this option remains non-viable for cats due to their very tiny nares, which are too small to accept the nasal prongs and minimally invasive oxygen therapy for cats remains centred around the use of an oxygen cage.

Looking to the future

The COVID-19 pandemic has generated renewed interest in producing affordable and portable ventilators, as well as less invasive forms of respiratory support. There is much we can still learn about how best to treat ARDS patients, without causing further injury to the lungs. Without a doubt, ongoing improvements in technology will enable us to further tailor respiratory support to individual patients, both furry and hairless alike, to maximise oxygenation and ventilation efficiency, whilst minimising VILI.

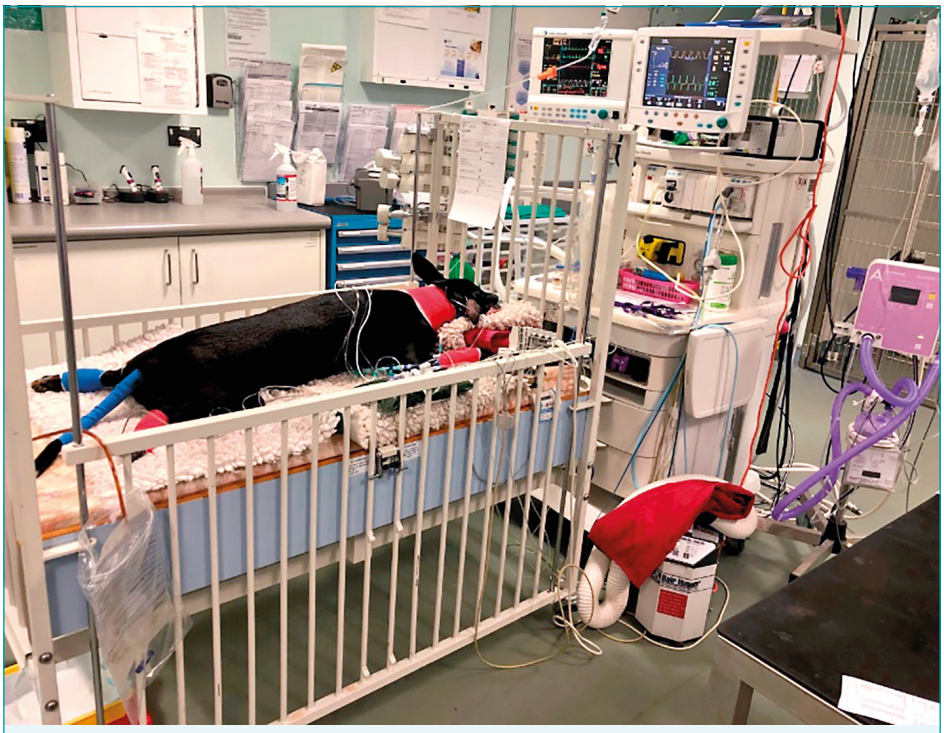

Figure 3. Prone positioning of a dog being mechanically ventilated. The dog is fully instrumented with an invasive arterial line for blood pressure and arterial blood gas monitoring, a jugular line for delivery of drugs and fluids and a urinary catheter for monitoring urine output and fluid balance. The right side of the ventilator screen shows the ventilator parameters and the left side shows the patient parameters. The pink device at the right of the photograph is a high-flow oxygen unit, which the dog was on prior to initiating mechanical ventilation.

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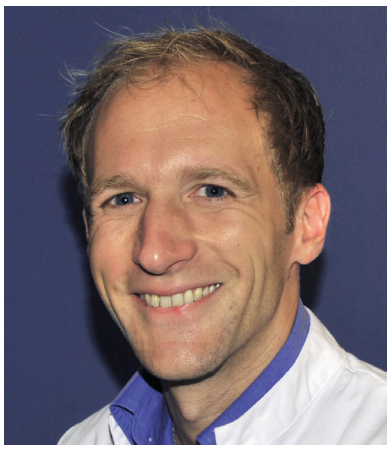
Remote heart rhythm assessment by a smartphone camera

How a mobile app made the difference during the COVID-19 pandemic



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The Maastricht University Medical Center (MUMC+), is renowned for the management and treatment of patients with atrial fibrillation (AF). AF is the most prevalent cardiac arrhythmia. A progressive atrial remodelling process mainly characterised by atrial dilatation, cardiomyocyte hypertrophy and fibrosis, which creates a substrate to stabilise the arrhythmia. Additionally, ectopic discharges originating in the pulmonary veins can initiate and maintain AF episodes.

The treatment of AF patients involves the management of concomitant conditions such as hypertension, heart failure and obesity. Additionally, pharmacological treatment (by antiarrhythmic drugs) and catheter-guided electrical isolation of the pulmonary veins help to maintain sinus rhythm. To reduce ventricular rate during AF, beta-blockers, L-type calcium channel blockers and digoxin are used to control AF symptoms and to prevent tachycardia-associated complications.

AF is associated with morbidities such as heart failure and an increased risk of thromboembolic complications such as stroke, as well as mortality (Hindricks *et al.*, 2020). Patients with AF are considered vulnerable and therefore monitoring of vital parameters, particularly heart rate and rhythm, is crucial to guide treatment decisions. A ventricular rate above 110 bpm during AF may lead to symptoms such as palpitations, dyspnoea, and may ultimately contribute to the development of heart failure (tachy-cardiomyopathy).

Under normal circumstances patients with AF will receive a face-to-face consultation in the outpatient clinic at the MUMC+. Prior to the consultation, an ECG is performed so that heart rate and rhythm information is available. During the coronavirus 2019 (COVID-19) pandemic, this was not possible. Social distancing was implemented to prevent extensive spread of the virus (or "flattening the curve", as we've all come to know it). To protect our AF patients from being infected by COVID-19, face-to-face outpatient appointments were rapidly converted into teleconsultations, resulting in the proportion of patient contacts managed by teleconsultations increasing from fewer than 1% in 2019 to 76% in 2020. This meant that instead of seeing our patients with ECG information, we were calling them without any clinical data about heart rate and rhythm and it became clear that treatment decisions were going to be difficult.

Obtaining rate and rhythm information from patients at home

Prior to the COVID-19 pandemic, we were conducting some smaller research projects using mobile health (mHealth) technologies for remote heart rate and rhythm monitoring (Hermans *et al.*, 2020; Hermans *et al.*, 2021). Some of these mHealth devices are based on a single-lead ECG, whereas others base their heart rate and rhythm assessment on photoplethysmography (PPG) (Fig. 1) (Hermans *et al.*, 2020).

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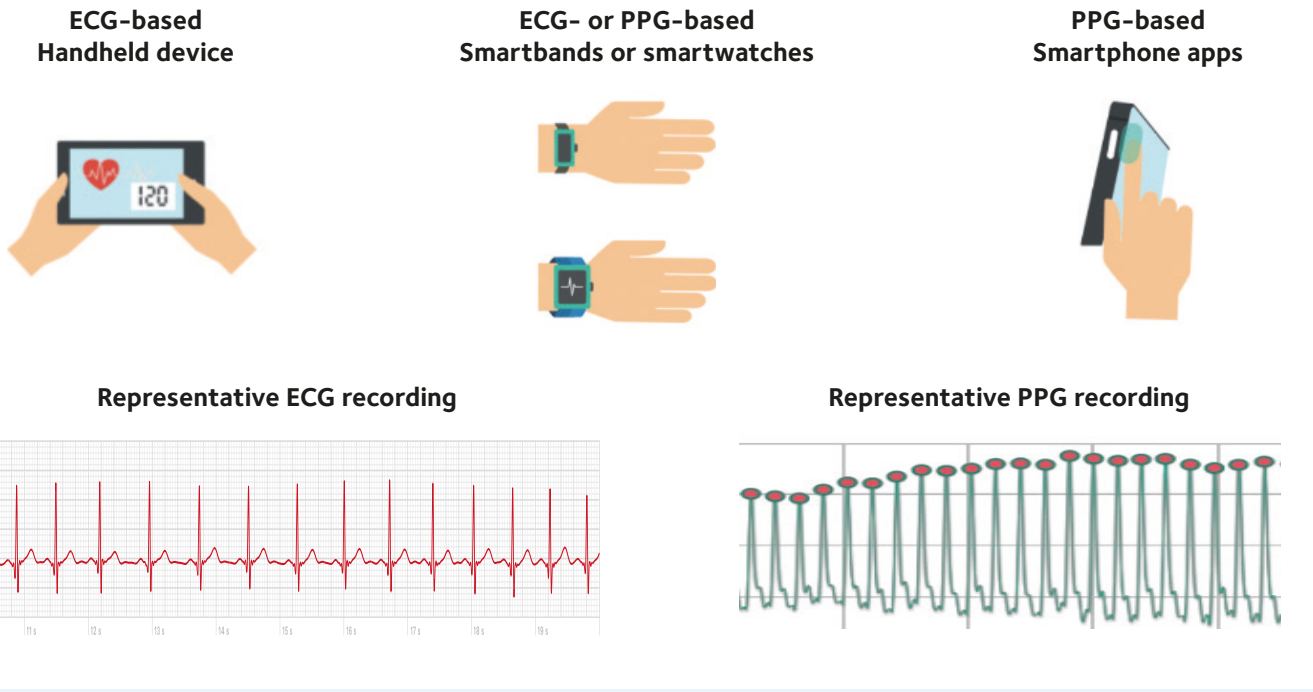

Figure 1. Different mHealth devices and the representative ECG and photoplethysmography (PPG) rhythm recording. The devices shown here represent the Alive Core device (a fitness tracker), the Apple watch and a smartphone with an application that uses the built-in camera and PPG technology.

Traditionally, the cardiac electrical activity visualised by an ECG is the gold standard to assess the cardiac rhythm; however, emerging PPG technologies represent an alternative strategy. Clinically, PPG is currently used for finger pulse oximeters to measure oxygen saturation. Additionally, PPG can determine blood volume pulse variation in the local arterioles of the fingertip by measuring the amount of reflected light by a camera. There are applications available that convert the 60 Hz video data to raw signals. In this way, each individual pulse wave can be detected. The time intervals between consecutive pulse signals can be used to determine the heart rhythm and differentiate normal sinus rhythm from an arrhythmia such as AF (Fig. 2).

The differences in PPG and ECG technologies have important implications. Current AF guidelines of the European Society of Cardiology (ESC) state that ECG documentation, either on standard 12-lead ECG or on a single-lead ECG tracing, is required to establish the diagnosis of AF (Hindricks *et al.*, 2020). Although PPG technology cannot be used to diagnose AF, it is able to accurately detect AF episodes. Several studies have been performed to determine the accuracy of PPG-based devices to detect ECG-confirmed AF. A meta-analysis by O'Sullivan *et al.* including four PPG-based mHealth devices presented an overall sensitivity and specificity of 94.2% and 95.8%, respectively (O'Sullivan *et al.*, 2020). Therefore, PPG technology can be of great value in remotely assessing cardiac rates and rhythms to support management of

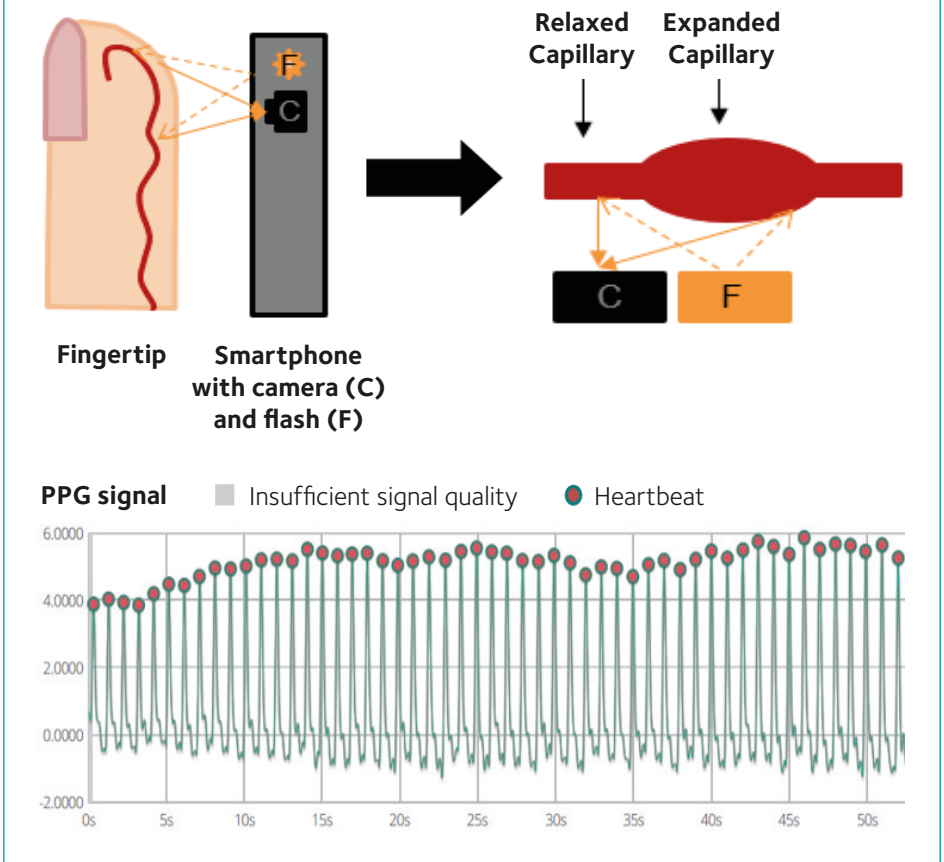

Figure 2. The principle of photoplethysmography (PPG) rhythm recording: A light source, for example the flashlight of a mobile phone, emits light onto the capillaries in the fingertip. The reflected light is then detected by a photo detector, for example the camera of a smartphone. The variations in reflected light intensity mirrors the blood pulse variation (below) and can be used for rate and rhythm assessment.

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Figure 3. PPG recordings are performed by the patient by a built-in camera of a mobile phone and transferred via a cloud to the hospital. In the hospital, the recordings are available via the physician dashboard.

"We literally turned smartphone technology, which is available to every individual, into a medical device to provide vital information to the clinicians required for remotely treating patients"

patients who have been previously diagnosed by ECG with specific arrhythmias such as AF.

Additionally, the wide availability and affordability of PPG technologies (e.g. using smartphone camera) can be used in effective and economical AF screening programmes in patients with unknown AF to minimize the potential for harm in terms of inappropriate treatment (anticoagulation leading to an increased risk of major bleeding) and unnecessary investigations; maximising the diagnostic yield of AF that carries significant risk; and maximising the uptake of appropriate anticoagulation treatment in people with newly detected cases.

Our approach: TeleCheck-AF

While PPG technology has limitations for diagnosing AF, the wide accessibility and low cost of this technology – via smartphone apps using the built-in camera and flashlight of a mobile phone – made it an optimal tool for remote heart rate and rhythm monitoring of patients who have already been diagnosed with AF by ECG documentation. We literally turned smartphone technology, which is available to every individual, into a medical device to provide vital information to the clinicians required for remotely treating patients (Pluymaekers *et al.*, 2020).

During the COVID-19 lockdown period, we contacted our AF patients 1 week prior to a scheduled teleconsultation and instructed them to download an app called FibriCheck (Conformitè Europëenne [CE]-marked and Food and Drug Administration [FDA]-approved), www.fibricheck.com). The patients were educated to perform three rate and rhythm recordings a day until the teleconsultation, and additional measures in case of symptoms. All recordings were instantly transmitted to a secured cloud system, which was accessible to the physician at the time of the teleconsultation (Fig. 3). We called this on-demand mHealth intervention: TeleCheck-AF (Pluymaekers *et al.*, 2021; Linz *et al.*, 2020).

TeleCheck-AF went viral during the COVID-19 pandemic

We started to communicate about our approach via Twitter (using the hashtag #TeleCheck-AF) and it was featured as an example of how to keep patients out of hospital using remote rhythm and rate monitoring by the European Society of Cardiology. We then implemented the TeleCheck-AF approach in numerous European centres during COVID-19. As a result of scaling up our activities, an additional 39 centres in 14 European countries were on-boarded to the TeleCheck-AF project. In total, 2,878 patients (including the patients in MUMC+) have been managed by the TeleCheck-AF approach outside the hospital remotely via teleconsultation (Fig. 4). This has reduced the burden for outpatient clinics and potentially reduced the risk to get infected by COVID-19 in a lot of patients. To assess how mHealth was used within the European TeleCheck-AF project, we are currently performing a retrospective analysis in most of the participating centres (Linz *et al.*, 2020).

The next steps in remote AF management

According to current AF guidelines, AF management does not just involve rate and rhythm assessment. In addition to rate and rhythm control, the assessment

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and management of risk factors is also critical. Longitudinal monitoring of lifestyle factors and vital signs may impact how we manage our patients remotely in the future (Hermans *et al.,* 2020; Gawalko *et al.,* 2020). Already, smart wearable devices can capture important biometrics, which could help assess risk factors and lifestyle components longitudinally to initiate and guide risk-factor-modification programmes remotely.

Physical activity can be captured by using medical grade actigraphy via GPS and accelerometers to monitor the change in fitness (for example by www.fitbit.com). Lifestyle factors such as diet can be assessed in digital diaries (for example by www.Lumen.me or www.foodmarble.com). Some preliminary studies suggest that PPG signals recorded by mobile phones and watches can be calibrated against non-invasive blood pressure to monitor relative changes in blood pressure (www.mypblab.com). Additionally, several smartphone and smartwatch apps are starting to provide information about sleep patterns, quality and duration of sleep, by detecting variations in oxygen saturation and generating hypnographs (www.fitbit.com), as well as detecting interruptions in snoring patterns, which may be indicative of sleep apnoea (www.snorelab.com). Other devices or apps have been developed to capture and track biometrics related to breathing, such as measuring respiratory rate using impedance. Peripheral arterial tonometry (PAT) is currently used to detect respiratory events during sleep by measuring pulse oximetry desaturations. Also autonomic nervous system activation can be approximated. The quantification of sympathetic discharges can be assessed by a PAT amplitude reduction and concomitant increases in heart rate. These technologies may help to detect sleep-disordered breathing, an important modifiable risk factor for AF, in large patient populations in the future (Linz *et al.,* 2018). Finally, hypoxaemia during daytime detected by oximetry is suggestive of lung disease such as chronic obstructive pulmonary disease, which is related to increased risk of AF and lower response to AF treatment strategies (Simons *et al.,* 2021). Although several apps and wearables provide multiple biometrics that can be used for risk assessment and monitoring of treatment response, most apps are not CE-marked or FDA-approved and additional validation studies are required.

Clinical implementation and achieving digital equity

Smart wearable devices and smartphone apps used by our patients will provide more and more biometric information, which may guide our treatment decisions in the future. Despite the rapid progress of technology, there is still a significant gap between what we know and how we apply that knowledge in clinical practice. Therefore, it is crucial to invest in implementing this technology in existing clinical care pathways and apply that knowledge in the clinic. In addition to supporting the development of suitable mHealth infrastructures in the hospital, we also need to involve our patients in this process: a focus on education and empowerment to support self-care is crucial. The absence of reimbursement models and privacy considerations are the main reasons that mHealth use is currently largely patient-initiated. This leaves the patient with the difficult choice of deciding which device to use. Not all patients may be able to pay for the expensive devices or monthly fees to use a specific app. We as scientists, physicians and society need to make sure that the new technology is accessible and user-friendly to all patients, to ensure digital equity in mHealth and throughout modern medicine.

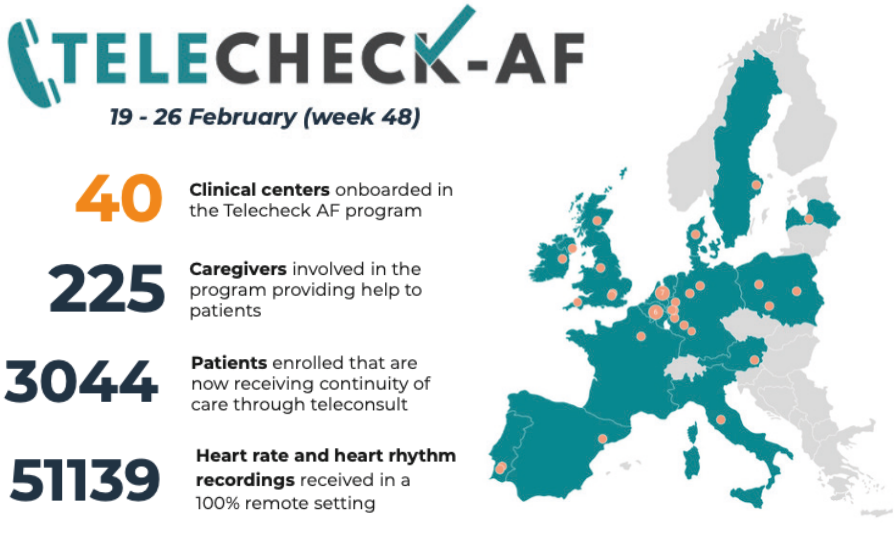

Figure 4. Numbers of TeleCheck-AF. Summary of centres participating in TeleCheck-AF.

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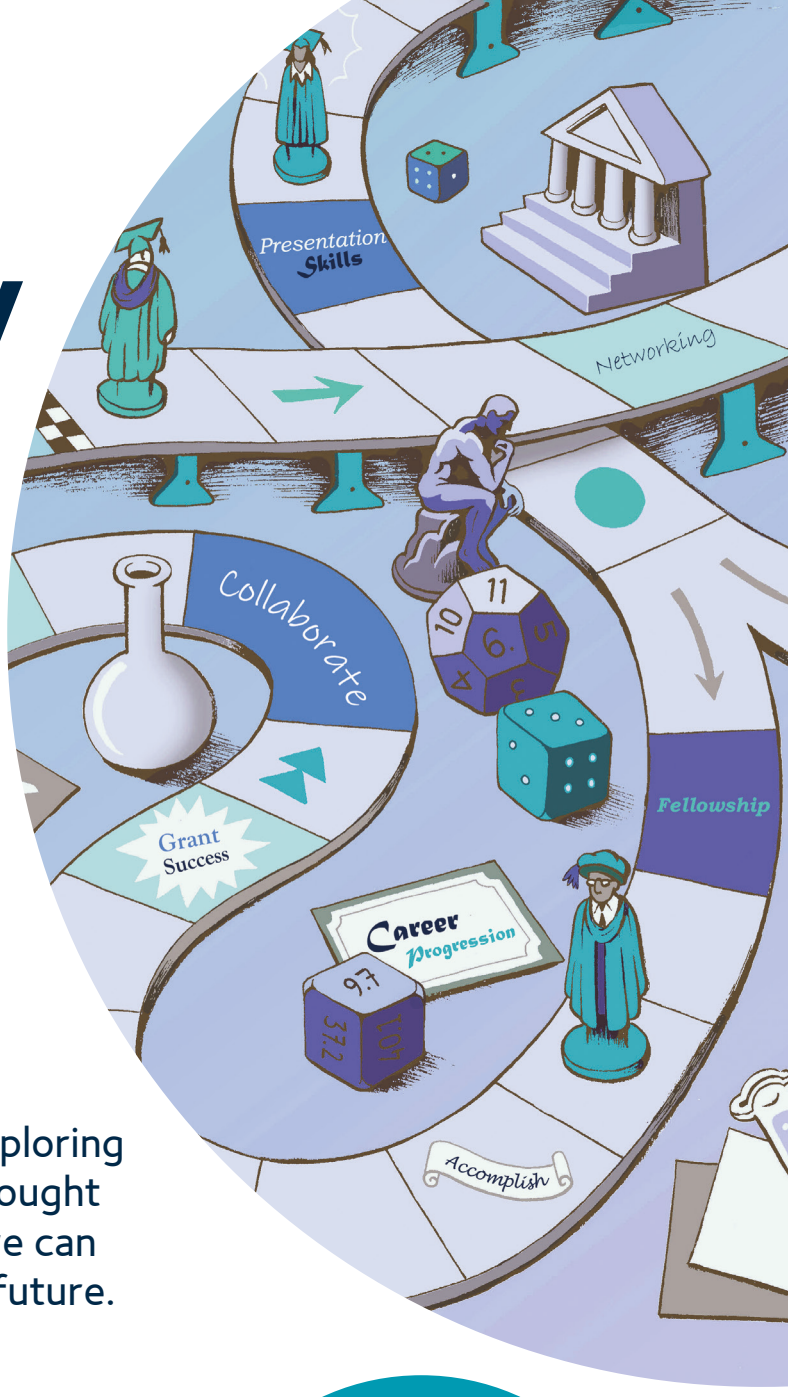

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Time is of the essence

Thrombolysis and thrombectomy treatment of acute ischaemic stroke

Rosanna Rossi, Andrew Douglas, Ciara Tierney & Karen Doyle

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Stroke, a leading cause of death and disability worldwide, is caused by deprivation of oxygen and nutrient supply to the brain, resulting in loss of brain cells within minutes, and causing neurological dysfunction. About 15% of strokes are haemorrhagic, but the majority (85%) are ischaemic attacks, caused by blockage of a cerebral vessel by a blood clot. Over 100,000 people in the UK and 10,000 people in Ireland suffer a stroke per year, with a mortality rate of approximately 40% (NICE, 2019; National Office of Clinical Audit, 2019).

Prior to the late 1990s, there was a lack of specialist acute stroke treatment available. Over the last 20 years, acute ischaemic stroke treatment has improved considerably, first through the approval of a thrombolytic drug to dissolve blood clots, and more recently through the development of mechanical thrombectomy as an intervention to remove the clot.

Thrombolysis

Blood clots form in response to vessel injury in a process that starts with formation of a loose platelet plug, followed by activation of the coagulation cascade resulting in formation of a fibrin mesh that strengthens the clot. Clot breakdown occurs through the activation of the zymogen plasminogen to form plasmin, a serine protease that is a powerful fibrinolytic. Plasmin cleaves fibrinogen and fibrin-rich diffuse networks in clots, thereby dissolving the clot (NINDS tPA Study Group, 1995). Cleavage of plasminogen to form plasmin occurs through the action of tissue plasminogen activator (tPA), which is slowly released by endothelial cells at the site of injury.

The first paper investigating the potential of a thrombolytic agent as a stroke treatment was published in 1958 (Sussman and Fitch, 1958). In this paper, Sussman and Fitch treated three patients with intravenous plasmin over a period of 6 days, leading to notable symptomatic improvement in one patient. However, due to increased risk of intracerebral haemorrhage, for many years the potential of thrombolytic agents to treat acute ischaemic stroke was not advanced to the clinic.

This changed in 1995, when a key clinical trial proved tPA to be beneficial (NINDS tPA Study Group, 1995). Subsequent approval y the US Food and Drug Administration (FDA) in 1996 led to the first major clinical development in the treatment of acute ischaemic stroke. Alteplase is a recombinant form of tPA (rtPA), identical to the tPA produced by endothelial cells in the human body. Alteplase has a very short life of 4-6 minutes, so it must be administered intravenously, and it is approved to treat stroke worldwide in an acute care setting. Alteplase minimises the likelihood of disability 3 months after treatment by 30%. Related thrombolytics, such as tenecteplase, which is a tPA variant that has a longer half-life, which can be administered as a bolus injection and also has greater fibrin specificity.

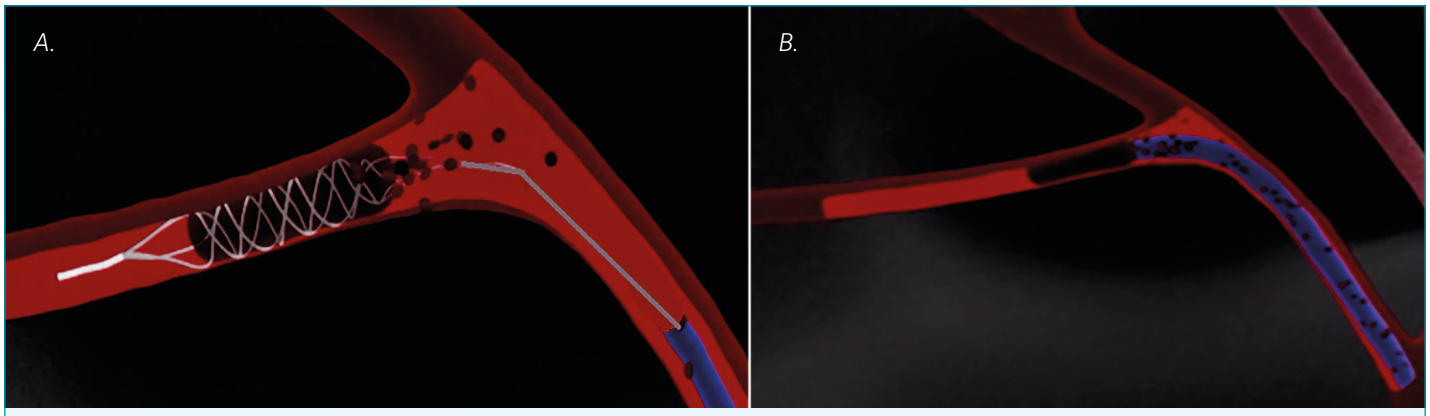

Figure 1. A schematic representation of thrombus removal by mechanical thrombectomy with *A.* a stentriever device and *B.* an aspiration catheter. (Source: *A Tiny Spark* (2018). Directed by Niamh Heery, Republic of Ireland: Swansong Productions. Available at: https://swansongfilms.ie/documentaries/tiny-spark/. All rights reserved by Swansong Productions.)

Figure 2. Images of acute ischaemic blood clots demonstrating the heterogeneity of the clots, ranging from red blood cell-rich clots (dark red/brown) to fibrin/platelet-rich white clots.

"Although many developments have occurred since the first stentriever prototypes, the general way they work remains the same"

Tenecteplase is not yet approved for acute ischaemic stroke treatment worldwide although clinical trials are ongoing and promising.

Although tPA was, without doubt, a paradigm shift in acute ischaemic stroke treatment, it has some limitations and drawbacks, notably increased risk of haemorrhage. There is a short safe window for treatment in eligible patients (4.5 hours from onset of symptoms), resulting in only a small number of stroke cases being treated. In Ireland, current data shows that only 11% of acute ischaemic stroke cases receive thrombolysis (National Office of Clinical Audit, 2019).

Thrombectomy

The procedure of mechanical thrombectomy involves introducing a medical device into the vasculature via the groin, and threading through the heart to reach the cerebral vasculature. There are two main types of medical device used: aspiration catheters and retrievable stent devices (known as stentrievers) (Fig. 1). In 2015, five separate randomised, controlled clinical trials using early prototype devices for mechanical thrombectomy showed positive results in acute ischaemic stroke patients with large vessel occlusions (Palaniswami and Yan, 2015). In 2019, 9% of people who had an acute ischaemic stroke in Ireland received thrombectomy treatment (National Office of Clinical Audit, 2019), an increase from 7% in 2018. In the UK, in 2017, only 1% of acute ischaemic stroke cases had thrombectomy, with the intent to increase to 10% as soon as possible (NICE, 2019).

Aspiration

In aspiration thrombectomy, a catheter of appropriate internal diameter is advanced to the occluded vessel and the distal end of the catheter is placed proximal to the clot (Fig. 1B). A negative pressure is applied via syringe or pump and the clot is suctioned into the catheter. Historically, the use of direct, also known as contact, aspiration in acute ischaemic stroke treatment was limited by the lack of catheters large enough to provide sufficient aspiration, yet flexible and atraumatic enough to navigate the tortuous intracranial vasculature. With newer aspiration catheters, these obstacles have been overcome, prompting the inclusion of aspiration alone as a valid alternative treatment for stroke.

Stentrievers

The first generation of retrievable stent devices were minimally invasive, catheter-based devices designed to physically entrap the clot to facilitate its removal. Although many developments have occurred since the first stentriever prototypes, the general way they work remains the same. First, a microcatheter crosses the clot, and then, as the retrievable stent is unsheathed from the microcatheter, it deploys, integrating into the clot. After a short time (typically 2–4 min) of allowing the stent to interact with the clot, the stent and microcatheter are retrieved,

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pulling out the clot (Fig. 1A). Although still very new, developments in stentriever design have improved thrombus–stent interaction, leading to better recanalisation rates and better patient outcomes.

Stentrievers and aspiration catheters can be used individually or in combination. The combined approach has recently shown success, although the cost involved of using multiple devices may be prohibitive.

Future therapeutic strategies for acute ischaemic stroke pathology

The future of acute ischaemic stroke treatment depends on the success of two research-led approaches. The first approach is to improve our understanding of the molecular mechanisms of brain injury caused by stroke, ultimately leading to neuroprotective drugs. This is the holy grail, but it is not likely to be realised imminently.

A second approach, to improve understanding of the cerebrovascular aspects of stroke, could lead to the discovery of new therapeutic targets and stroke prevention strategies in a shorter timeframe. Furthermore, research to improve the therapeutic strategies that are already available, such as further improvements in thrombolytics as well as novel and more effective thrombectomy medical devices will improve acute stroke treatment within a very short timeframe, saving many lives, and improving the quality of life for many others and their families.

Retrieval of the clots that cause strokes has afforded researchers the opportunity to study their composition using histology and immunohistochemistry. Not all clots that cause strokes are the same. The main components in a blood clot are red blood cells, fibrin, platelets and white blood cells. However, the proportions of these main components can vary considerably (Fig. 2). Clots range from being red blood cell rich, with loose fibrin stands providing the scaffold to hold the structure together, to containing almost no red blood cells, instead densely packed with fibrin strands and platelets. Some clots contain other components such as collagen, and others are calcified.

The composition of the clot significantly influences the outcome for patients treated with both rtPA and mechanical thrombectomy devices. For example, there is evidence that clots that are red blood cell rich with loose fibrin strands respond best to tPA, which effectively reduces the size of those clots, while other clots are tPA resistant, and need to be removed by mechanical thrombectomy (Rossi *et al.*, 2020). Other recent work in our lab has found that clot composition varies with stroke aetiology (Fig. 3) (Fitzgerald *et al.*, 2020). There are still many unanswered questions, and much left to learn. Further interrogation of the clots that cause strokes will help to advance understanding of the causes of stroke, the pathophysiology of the cerebrovasculature in stroke and advance medical device design for even the most difficult to remove clots, improving acute stroke care.

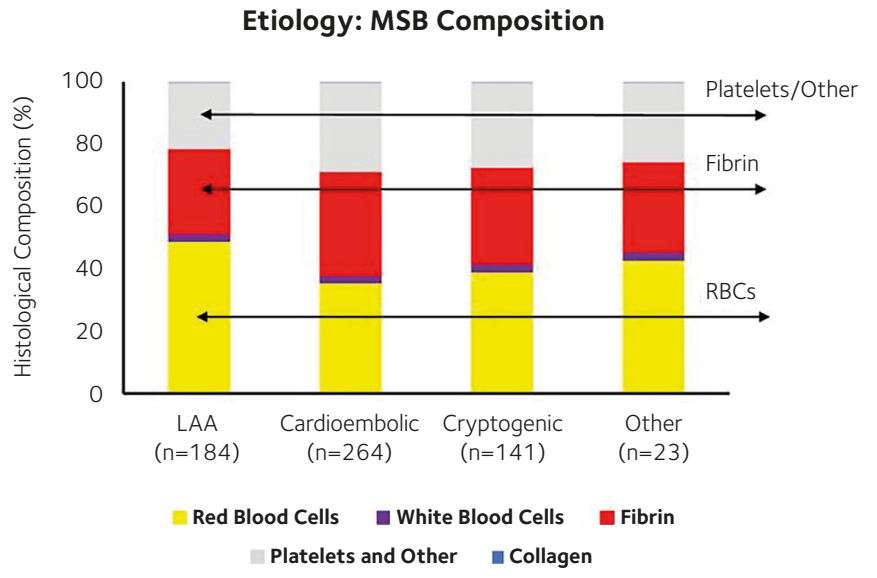

Figure 3. Histological clot composition per histological component by suspected aetiology, as assessed by Martius Scarlet Blue staining (MSB). Abbreviations: LAA, large artery atherosclerotic (clots); RBCs, red blood cells. © Fitzgerald S *et al.* (2020).

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Artificial blood transfusion

A new chapter in an old story

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Among bodily substances, blood is particularly prominent. Conspicuous by its crimson colour, it not only permeates our bodies but also our societies and cultures, from religious customs to vampire literature to crime dramas. Our fascination with blood is unsurprising given that it plays crucial roles in our bodies (e.g. in transportation, homeostasis, and defence). And yet, despite around 118.5 million blood donations globally, the supply of this most ubiquitous of substances is often outstripped by demand. One solution to this shortage is the mass manufacturing of artificial substitutes, but many of these have failed to meet the safety standards and physiological needs, until recently.

As every physiology undergraduate learns, the centrifugation of blood reveals that it consists of three components: red blood cells (RBCs); a buffy coat that contains white blood cells (WBCs) and platelets; and plasma. RBCs contain haemoglobin (Hb) and work as a gas carrier, transporting oxygen and carbon dioxide between the lungs and tissues, as well as a pH buffer. WBCs recognise and remove foreign invaders, while platelets promote blood clotting. Together they maintain haemostasis and orchestrate our immune defences. Plasma, though mostly water, also contains proteins (e.g. albumin, globulin, and fibrinogen) and other solutes (e.g. gases, ions, and hormones), one of the most important of which is albumin, which maintains colloid osmotic pressure and blood volume essential for haemodynamic stability.

Given these vital functions, the anticipated effects of blood loss (haemorrhage) on our bodies are adverse. Indeed, depending on the degree of bleeding, haemorrhaging patients experience what clinicians refer to as "shock", namely a drop in blood pressure (hypotension), a rise in heart rate (tachycardia), hypovolaemic-induced hypoperfusion of tissues, and a subsequent a lack of cellular oxygen delivery (ischaemia). In such cases, rapid fluid infusion and blood transfusion are required to replenish the lost components and restore haemodynamic stability and oxygen supply. Whilst transfusions are simple (blood from one person is transferred to another's circulation intravenously), they remain indispensable for treating patients suffering from severe bleeds, anaemia, and cancer. In fact, it can be said that blood transfusions are a kind of cell therapy or tissue transplant (it is technically a connective tissue after all). It's useful, therefore, to consider the history of blood transfusions, and how advancements in this therapy can save lives.

The history of blood donation

The transfusion story starts in the 1800s with the British obstetrician Dr James Blundell. Practising in London, Dr Blundell first implemented transfusion (using fresh, whole human blood) for the treatment of post-partum haemorrhage (i.e. excessive

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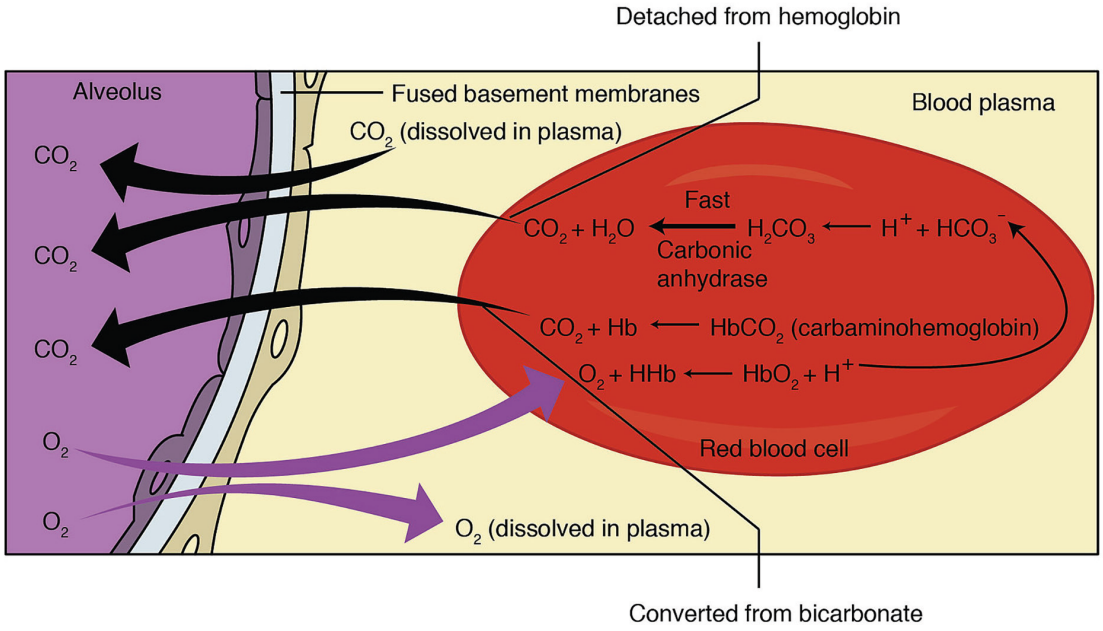

Figure 1. Roots and mechanisms of gas exchange for blood. (Illustration from Anatomy & Physiology, Connexions Website. http://cnx.org/content/col11496/1.6/ This image is licenced under CC BY 3.0.)

bleeding after childbirth; Blundell, 1829). He later demonstrated that haemophilia (a rare genetic disease that affects blood clotting) could be managed in a similar way. Despite these advances, transfusions persisted at the periphery of medicine for some time, mostly owing to a high risk of death. It wasn't until the discovery of distinct human blood types in 1901 that the lethal complications of mismatched blood typing were resolved.

During the 20th century, great efforts were made to adapt the extraction and processing of blood, improving its long-term storage capacity and increasing its clinical adoption. For example, anticoagulants made it possible to safely store donated blood in a stable condition. Centrifugation enabled the fractionation of blood into its constituent parts. Once RBCs, WBCs, platelets, and plasma were able to be sorted and stored, they could be used independently, giving rise to component transfusion.

Now, the technology has developed further to fractionate albumin, globulins, and fibrinogen from plasma. Nevertheless, the contamination of donated blood by pathogens (e.g. hepatitis and HIV) remains an issue. Today, medical interviews of donors and advanced blood screening help ensure that most transfusion-transmitted infections are prevented. However, new emerging pathogens (e.g. SARS-CoV-2) threaten the present blood donation and transfusion system.

Honing blood transfusion techniques

Fluid treatment (including component transfusion) has saved many patients from haemorrhagic shock. And yet it can also increase dilutional coagulopathy (i.e. an impairment of blood clotting following the dilution of platelets in large volumes of fluid). To mitigate this, the concept of balanced transfusion has been introduced in the US whereby RBCs, platelets, and plasma are administered at a unit ratio of 1:1:1 in the early stages of transfusion (including prehospital transfusion; Holcomb *et al.*, 2015). However, such fluid delivery of three components is not easy to prepare promptly, owing to the different storage conditions of each (e.g. packed RBCs are readily available from a refrigerator, but fresh frozen plasma takes at least 30 minutes to thaw before use). Likewise, logistical limitations exist because of the different shelf-lives of RBCs (3–6 weeks) and platelets (3–4 days); plus, platelet concentrates require shaking at 20–24°C for preservation. This complex situation makes it hard for clinical staff to administer urgent transfusions simultaneously. Moreover, component transfusions require specific preservative solutions for each component, and severe trauma patients need to receive additional fluids (e.g. antibiotics, inotropes, nutrients). This non-negligible volume of fluids can cause a further rise in volume, leading to worsened dilutional coagulopathy and patient outcomes.

The use of blood transfusions are further complicated by the various inflammatory responses and organ damage they may evoke in the hosts. For example, Transfusion-Related Acute Lung Injury (TRALI) and Graft-versus-Host Disease (GvHD). To avoid such immune reactions, several modalities have been adopted, such as the irradiation of blood products.

Additionally, a recent paper demonstrated the enzymatic conversion of type A to type O blood (Rahfeld and Withers, 2020), which has the potential to boost the amount of the universal blood donor type available and minimise the risk of adverse reactions in those who receive it. As climate change continues, natural disasters will occur more frequently, and the care of mass casualties will become an inevitable consequence. Not only is it difficult to save a lot of injured victims of such events, but should the supply system of medical resources (including blood products) be broken, a larger number of fatalities will occur.

The future of blood transfusion: artificial blood

Hb has dual roles: oxyHb literally transports oxygen in the arteries and deoxyHb captures protons in the veins (a role important for pH buffering). The Bohr and Haldane effects are essential to these unique properties of Hb, whereby an increase of carbon dioxide in the blood promotes the displacement of oxygen from the Hb, and conversely the binding of oxygen to Hb during high oxygen concentration tends to displace carbon dioxide from the blood (Hall, 2015). Additionally, RBCs utilise the carbonic anhydrase to metabolise carbon dioxide into protons and bicarbonate for transportation. (Fig. 1).

Considering the current situation, additional innovation is required to improve blood transfusion as a therapy and make it more accessible to patients. Our laboratory is interested in the use of acellular Hb as a form of "artificial blood" to do just that given its unique properties.

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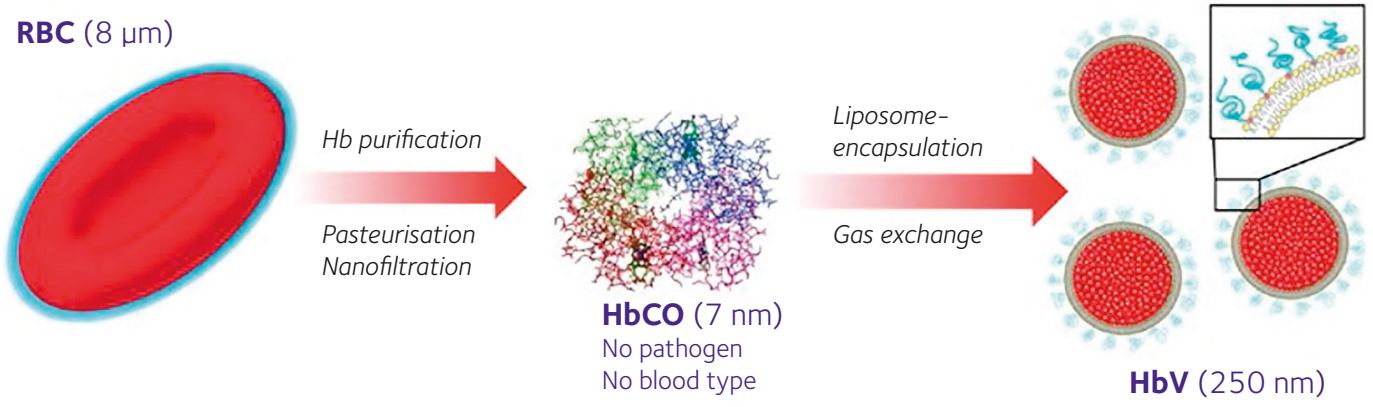
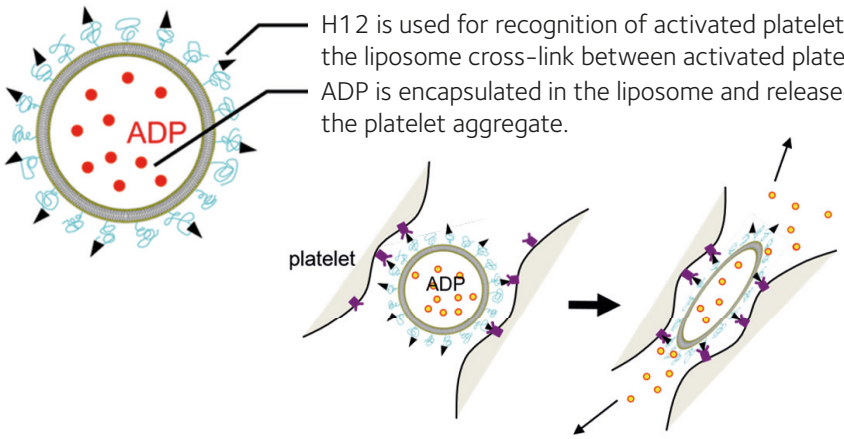


Figure 2. Preparation of haemoglobin vesicles (HbV) from outdated NAT (nucleic-acid amplification testing)-inspected red blood cells (RBC) provided by the Japanese Red Cross. The HbCO purification procedure includes pasteurization and nanofiltration for utmost safety from infection. Liposome encapsulation shields the toxic effects of molecular haemoglobin (Hb). © Sakai H *et al.* (2017). This image is licenced under CC BY 4.0.

Figure 3. H12-(ADP)-liposomes as platelet substitutes. The liposomes can cross-link between activated platelets and then release ADP, leading to promotion of platelet aggregation (Okamura *et al.*, 2009). [Image credit: Takeoka *et al.*]



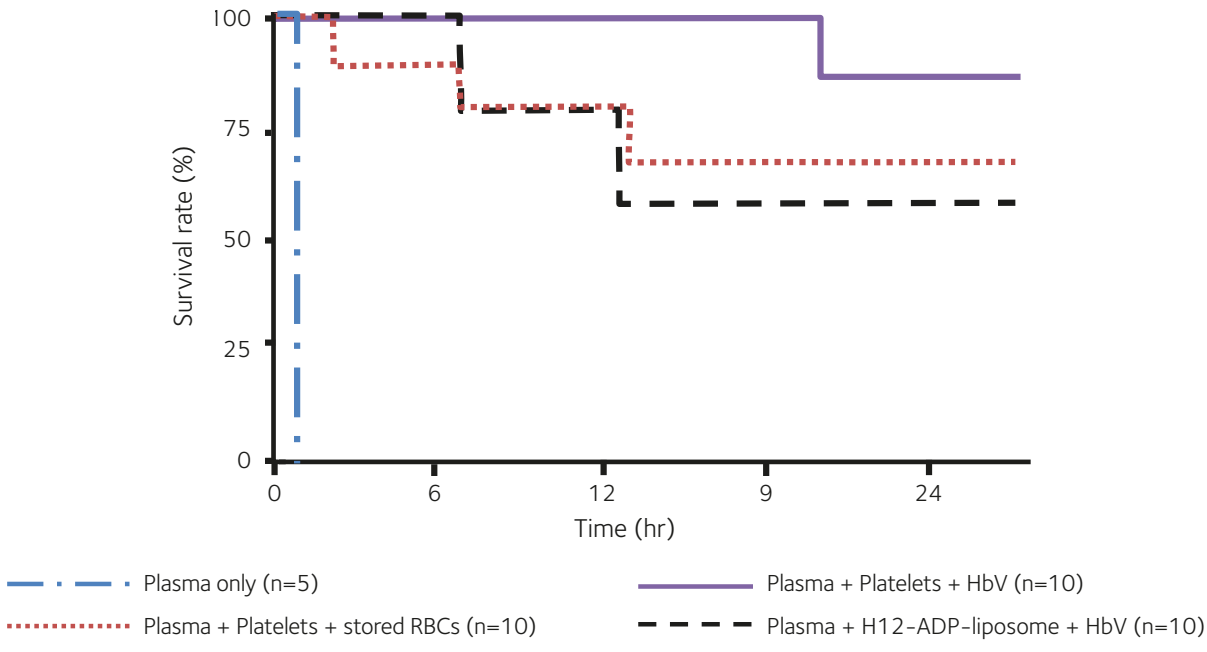


Figure 4. Survival rates of rabbits with induced acute thrombocytopenic/haemorrhagic shock. Balloon compression and administration of HbVs and H12-(ADP)-liposomes as well as RBC concentrate, and platelet-rich plasma rescued 60% to 70% of the animals after liver haemorrhage because of potent haemostasis at the liver bleeding site. Whereas those receiving only platelet-poor plasma had 0% survival in the first 24 hours. © 2019 AABB.

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"We demonstrated that, in combination with H12-(ADP)-liposomes, our HbVs helped to maintain both haemodynamics and haemostasis following severe traumatic haemorrhage with coagulopathy "

Purified Hb was first tested as a substitute for RBCs in transfusions in the 1930s. However, "naked" Hb caused renal toxicity and adverse cardiovascular effects (presumably resulting from scavenging of nitric oxide; NO). Since the 1970s, cross-linked Hb, recombinant Hb, and polymer-conjugated Hb have been developed. But, most failed to progress to clinical trials because the toxicities of cell-free Hb could not be completely eliminated. A third generation, consisting of polymerised Hb encapsulated within larger particles, have been developed recently by several researchers, including our group.

Our Hb vesicle (HbV) is a type of Hb encased in a liposomal capsule (Sakai, 2017) (Fig. 2). We believe it has several advantages as an artificial RBC, namely: it does not evoke a strong immune reaction; the scavenging of NO is minimal; it can be stored for long periods of time at room temperature; and to simplify the HbV production, we omitted the incorporation of carbonic anhydrase as transportation of carbon dioxide could likely be sufficiently handled by physical dissolution in plasma.

As for haemostasis, several researchers have also developed artificial platelets. Most are composed of small particles with surface modifications whereby the ligands for integrins on the activated platelets are added (Okamura *et al.*, 2009; Hickman *et al.*, 2018). Platelets made from induced pluripotent stem cells and adipose tissue-derived stem cells are also on the horizon. Our group has developed H12-(ADP)-liposomes (Okamura *et al.*, 2009), which accumulate at a bleeding site through interaction with activated platelets via glycoprotein IIb/IIIa and H12, and augment platelet aggregation by releasing adenosine diphosphate (ADP) from the liposomes at the bleeding site for activation of platelets within a few minutes. H12-(ADP)-liposomes remained intact in the blood circulation for up to 24 hours after injection if they do not meet with activated platelets at the bleeding site. ADP released in blood is immediately metabolised to allantoin and fully discharged to urine within 6 hours (Fig. 3). These H12-(ADP)-liposomes can even be stored for at least 6 months at 4˚C without shaking while conventional platelet concentrate must be used within 4 days and requires constant shaking at 22˚C.

In our recent animal study, we demonstrated that, in combination with H12-(ADP)-liposomes, our HbVs helped to maintain both haemodynamics and haemostasis following severe traumatic haemorrhage with coagulopathy (Hagisawa *et al.*, 2019). The outcomes were as good as that achieved with transfusion of allogenic RBCs and platelets, and this combination therapy drastically reduced mortality with no serious adverse effects observed (Fig. 4). We are pleased to announce that a phase 1 clinical study examining the safety of HbVs has just begun, and we look forward to the results.

New research also promises to advance this technology further. For example, the manufacturing of Hb encapsulated particles with carbonic anhydrase and superoxide dismutase/catalase to replicate the RBC function by maximising carbon dioxide transportation and free radical scavenging (Chang, 2017). Or mimetics like Erythromer, which better emulate RBC physiology, and also serve to inhibit methaemoglobin accumulation and NO sequestration (Pan *et al.*, 2016), which is critical for long-term maintenance of haemoglobin oxygen-carrying capacity.

In conclusion, the early support of the coagulation system as well as oxygen delivery is essential for damage control following trauma. We consider artificial RBCs and artificial platelets an ideal substitute for component balanced transfusion and whole blood transfusion. We think that these blood substitutes will prove useful for prehospital resuscitation as they should achieve easy reserve, avoid immunological reactions, and do not require cross-matching of blood type.

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The story of when kidneys fail

The evolution of haemodialysis technology

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The products of cellular metabolism accumulate in patients with chronic kidney disease with potentially toxic effects, and today there are around 3 million patients with chronic kidney disease treated by dialysis worldwide. The term dialysis was first introduced by the Scottish chemist Thomas Graham, who reported in 1861 that crystalloids could be separated from colloids in solution by using a vegetable parchment acting as a semipermeable membrane. Almost 50 years later, Abel and colleagues in Baltimore employed a "vivi-diffusion" apparatus using a collodion membrane, later termed "artificial kidney" to perform the first dialysis treatment in dogs. Today, renal replacement therapy is a standard component of any modern nephrology and critical care unit, and as technology progresses, we get ever closer to developing wearable and implantable miniaturised artificial kidney devices.

The first dialysis in a patient was performed by Haas in 1924 in Germany, using a collodion membrane and heparin anticoagulation, but he discontinued his trials in 1928 due to disappointing results. During the Second World War, acute kidney injury caused by rhabdomyolysis following crush injuries after bombings was recognised and this led to attempts to treat patients with both peritoneal dialysis and haemodialysis. Solute clearances with peritoneal dialysis were inefficient, and Willem Kolff in the Netherlands, who built a "rotating drum kidney" (Fig. 1) with a cellophane membrane, reported the first recovery of a patient with acute kidney injury treated by haemodialysis in 1945 (Kolff *et al.*, 1997). Although Kolff's dialyser could remove urea and other small solutes including potassium by diffusion, it could not provide ultrafiltration, and required the continued injection and then withdrawal of 50 mL blood aliquots. Neils Alwall in Lund, Sweden saw the potential for haemodialysis to become a life-sustaining treatment for patients with chronic kidney disease and led developments in both dialyser design and dialysis machine technology. However, chronic haemodialysis only became reality in 1960, when Scribner and colleagues designed an external arterio-venous by-pass made of Teflon® tubing, so allowing permanent access to the bloodstream (Fig. 2), and this was later improved in 1962 by the introduction of the arterio-venous fistula, first described by Cimino and Bresica (Agarwal *et al.*, 2019).

Although haemodialysis is now an established treatment for patients with chronic kidney disease, performed in hospitals, stand-alone satellite centres or at home, the 5-year survival of haemodialysis patients is less than that for many patients with some of the more common solid organ malignancies, with most deaths due to cardiovascular disease. Globally, the majority of patients are treated three times a week, with each haemodialysis

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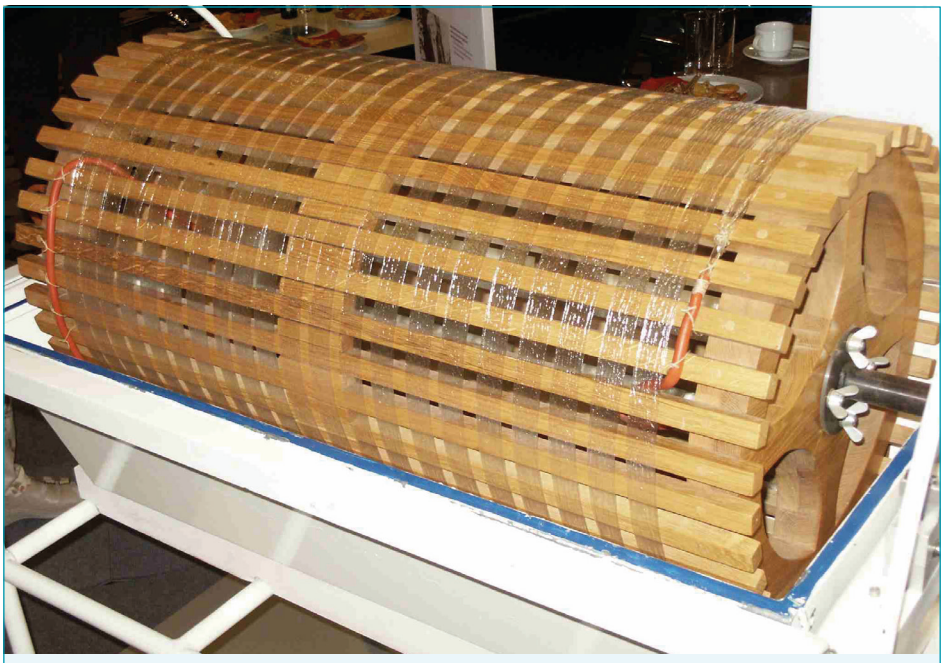

Figure 1. Kolf's "rotating drum kidney" first reported in 1945. The rudimentary dialyser could remove small solutes by diffusion but only in 50 mL blood aliquots at a time. Courtesy of Baxter Dialysis Historical Museum. Image credit: Andrew Davenport.

"In clinical practice, post-haemodialysis most patients leave the dialysis unit with some cerebral white matter oedema and increased brain water, a condition known as dialysis equilibrium syndrome"

session lasting around 4 hours, which is not only an "unphysiological" schedule compared with normal renal function, but also introduces iatrogenic (i.e. caused by medical treatment) adverse effects generated by direct contact of blood with the dialyser surface material and blood tubing. Although electrolyte balance and control of acid–base balance can be achieved by regulating the concentrations in the dialysis water, during dialysis there are major fluxes of electrolytes with potassium and magnesium moving out from the patient's blood, and bicarbonate and calcium moving from the dialysate into the patient's blood. These fluxes in electrolytes can lead to changes in the electrocardiograph, particularly lengthening of the QT interval, which may predispose patients to cardiac arrhythmias, typically supraventricular ectopics and atrial fibrillation.

A consequence of the "unphysiological" schedule of the sessions is the accumulation of metabolic waste products from the end of one haemodialysis session to the start of the next treatment. Urea, which is derived from protein catabolism and recycling of amino acids has the highest concentration of any of the retained solutes. As urea is a small uncharged molecule it can diffuse rapidly, and so is very efficiently cleared during haemodialysis. This is achieved by maximising the relative plasma and dialysis water concentration gradient with relatively fast countercurrent flows using a large surface area dialyser comprising narrow diameter capillary fibres.. So, plasma urea clearance is much faster than urea movement from the cells into the plasma. In addition, as haemodialysis has a catabolic effect, due to the inflammatory response induced by the contact of blood with components of the extracorporeal circuit, intracellular urea generation is increased during treatment. Water therefore moves back into cells to counter this concentration gradient, with water moving through aquaporin channels some 20–30 times faster than urea leaves cells by urea transporters. Therefore, in clinical practice, post-haemodialysis most patients leave the dialysis unit with some cerebral white matter oedema and increased brain water (Waltersl *et al.*, 2001), a condition known as dialysis equilibrium syndrome. Fortunately, most patients just feel tired, and take time to recover from the session, but occasionally patients may have a seizure or develop focal neurological signs.

Urea itself is not very toxic, as studies adding urea to the dialysis water to prevent the dialysis equilibrium syndrome exposed patients to very high blood urea concentrations without causing many of the symptoms associated with chronic kidney disease (Johnson *et al.*, 1972). Urea can dissociate in plasma water to cyanate, which can react with proteins to form carbamylated haemoglobin or carbamylated albumin. However, unlike glycosylation in diabetics, which can result in a permanently glycated Amadori end-product, carbamylation is a reversible process, and so levels rapidly fall post-dialysis. As urea *per se* is not thought to be the "toxic" waste product of metabolism that leads to the signs and symptoms of end-stage kidney disease, this led to the search for other waste products of metabolism that cause toxicity. The EuroTox group have identified more than 100 potential compounds (Vanholder *et al.*, 2008), and some of these potential toxins are of middle molecular weight, and not so readily removed by diffusion. For example, urea (64 Da) diffuses 18 times faster than β2 microglobulin (11,800 Da), so, one way of increasing larger solute clearances would be to increase the pore size of the dialyser membrane. However, simply increasing the pore size may then lead to increased losses of albumin, so there are technical issues to overcome to develop membranes that can allow diffusion of larger solutes but restrict albumin losses. An alternative is to add a convective movement of water, such that as blood is pumped through the dialyser a negative hydrostatic pressure is applied by the dialysis machine, and so water is pulled out from the plasma and any solute in the plasma water small enough to pass through the pores will now be removed with the water flux. So, with convection urea and β2 microglobulin are now removed equally, whereas with diffusion urea moves 18 times faster than β2 microglobulin. Combining diffusive and convective transport is termed haemodiafiltration, and studies (particularly those using higher volumes of convective clearance with haemodiafiltration) have shown greater patient survival, and in particular lower cardiovascular mortality for haemodiafiltration compared with standard haemodialysis (Nubé *et al.*, 2017).

However, not all of the potential toxins currently identified are free in plasma water to be readily cleared by dialysis, and those bound to proteins have limited clearance by dialysis. Some of these putative toxins, including indoxyl sulphate (IS) and trimethylamine N-oxide (TMAO) have been shown to be associated with endothelial damage and cardiovascular disease. Granting that dialysers can be redesigned to include sorbents to remove these compounds, this

https://doi.org/10.36866/pn.121.26

"A key objective of a dialysis treatment is to restore volume homeostasis and prevent left ventricular hypertrophy"

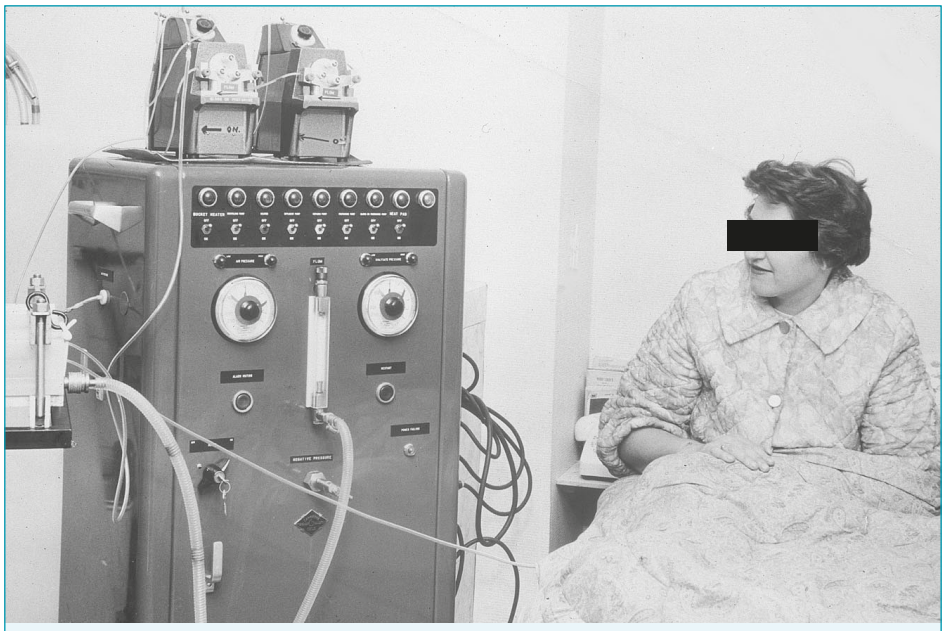

Figure 2. An example of the more advanced devices that emerged after innovations in the 1960s that made chronic home haemodialysis possible Courtesy of Royal Free Hospital. Image Credit: Dr Victor Gura

adds costs and complexity to manufacturing processes. However, as these compounds are derived from amino acid, choline, betaine, and carnitine metabolism by bacteria in the large intestine, therefore alternative ways of reducing these toxins are being investigated, as patients with chronic kidney disease who consume a plant-based diet have been reported to have lower levels of these protein-bound toxins (Kandouz *et al.*, 2016), and other potential toxins including deposition of advanced glycosylation end-products in the skin. Ultimately altering the gut microbiome by dietary interventions or medicinal compounds, or using absorbents to remove toxins, may be more practical ways of reducing these toxins.

In addition to the accumulation of waste products of metabolism, as patients may not pass any urine, patients gain weight from the end of one haemodialysis session to the start of the next session. Thus, a key objective of a dialysis treatment is to restore volume homeostasis and prevent left ventricular hypertrophy. Fluid weight gains are not limited to an expansion of the vascular compartment, as patients have a gain in extravascular lung water, and furthermore, magnetic resonance scanning has demonstrated an increase in both skeletal and cardiac muscle water content. Thus, during haemodialysis, fluid can only be removed from the plasma, but the majority of fluid gained between dialysis sessions is extravascular, so to maintain plasma volume the fluid has to move from extracellular and intracellular compartments in order to restore plasma volume. This compensatory refilling will depend on plasma tonicity (sodium and albumin concentration and haematocrit) and vascular permeability. However, for most patients there will be a contraction of the plasma volume following dialysis, as shown by a reduction in cardiac chamber sizes, as the rate of fluid removal from the plasma exceeds the refilling rate in the majority of patients (Kotecha *et al.*, 2019). As such, patients may then develop hypotension if their cardiovascular response cannot compensate for any reduction in effective plasma volume. At the start of dialysis, passage of blood across the dialyser membrane and through the extracorporeal circuit generates an inflammatory reaction with the production of complement, leukocytes, macrophages, and bradykinin, causing an initial leukocyte and platelet sequestration in the pulmonary capillaries with a reduction in oxygen saturation, which then resolves. In addition, blood supply to the skin, liver, mesentery, muscle, and kidney all fall, with blood pooling in the larger-capacitance veins. This can lead to an increase in body core temperature, and if the body overheats, can potentially lead to vasodilatation and hypotension. Accordingly, some centres cool the dialysis water to increase heat exchange thus preventing a rise in core body temperature.

In the UK, the median age of the haemodialysis population is now aged in their mid-60s, with almost 50% of patients having a diagnosis of diabetes, therefore cardiovascular regulatory responses may be impaired and intra-dialytic hypotension remains the most common complication of out-patient treatments. These changes in blood supply can lead to a reduction in perfusion of both the heart and brain, which reverse after the dialysis session has ended. As for the heart, episodes of reversible cardiac stunning, whereby a section of the left ventricle temporarily stops contracting,

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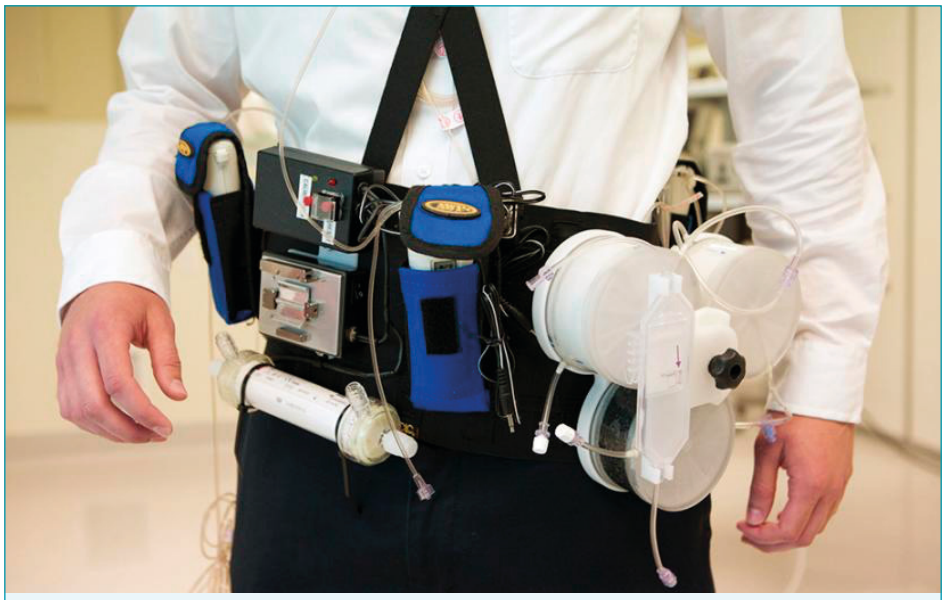

Figure 3. Protype miniaturised wearable artificial kidney (US Patent: US6960179). Containing reservoirs for electrolytes and bicarbonate supplements, pumps, blood –leak/bubble detectors, dialyser and regeneration unit. © Gura V *et al.* (2016). JCI Insight **1**(8):e86397 https://doi.org/10.1172/jci.insight.86397.

are more likely to occur in patients with pre-existing cardiac disease. Similarly, for the brain, a reduction in cerebral blood supply and increased areas of white matter ischaemia are more likely to occur in the older patient, and it is suggested that repetitive episodes of cerebral ischaemia may account for the rapid decline in cognitive function reported in elderly patients initiating haemodialysis. However, this decline in cognitive function may not just be limited to the older patient, as cognitive function did not improve following renal transplantation in patients who had been treated by haemodialysis for more than 3 years. In addition, haemodialysis patients have a 10-fold increase risk of ischaemic stoke compared with the general population (Findlay *et al.*, 2015). Whether this risk is due to the high prevalence of pre-existing hypertension, or due to the rapid changes in blood pressure during dialysis, remains to be determined.

If many of the adverse effects of haemodialysis are due to the intermittent nature of the treatment and rapid changes in solutes and reduced tissue blood supply, then daily treatments or continuous treatments could potentially improve patient outcomes. Indeed, more patients die after the longer weekend break between dialysis session. Studies using implantable cardiac monitors suggest that most deaths are associated with bradyarrhythmias, thought to be induced by the combination of hyperkalaemia and volume overload due to the greater time between dialysis sessions in the three times a week dialysis schedule. The Frequent Hemodialysis Network (FHN) study investigated the effect of dialysing 6 days a week compared with the conventional three-times per week paradigm (Tamura *et al.*, 2013). Two trials were conducted: one comparing short daily dialysis and the other longer nocturnal sessions, both against the standard schedule. Although the short daily haemodialysis trial showed an improvement in left ventricular mass for those who initially had left ventricular hypertrophy, no benefits were observed on depression or nutrition. In particular, there were no benefits observed in terms of psychological performance, including attention, psychomotor speed, memory, or verbal fluency (Tamura *et al.*, 2013).

The alternative approach would be to develop a continuous form of haemodialysis (Davenport, 2015). Although a wearable device would not be suitable for all patients, an implantable device could potentially be offered to many. Investigators have considered designs based on the glomerulus and renal tubule structure. Studies to date have developed a highly permeable membrane design, similar to a storm drain in structure, producing a high-volume filtrate, but technical problems have yet to be overcome, in terms of developing a reliable implantable vascular access and then designing and constructing a filtration system to reabsorb the large volumes of fluid filtered by the nanomembrane. As such, greater progress has been made taking a conventional haemodialysis machine and then miniaturising the technology to develop a wearable device (Fig. 3). Initial safety trials have shown that such a device can be safe and, provided continuous clearance is maintained, it achieves middle molecule and protein-bound toxin clearance with patient recovery time being instantaneous (Davenport *et al.*, 2007). These devices have been tested for up to 24 hours, and further trials have been planned to extend treatment times up to 7 days, including treatment at home (Gura *et al.*, 2016).

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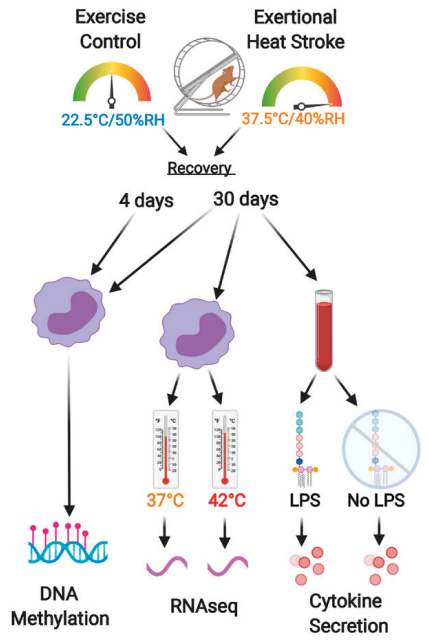
The Journal of Physiology

Exertional heat stroke leads to concurrent long-term epigenetic memory, immunosuppression and altered heat shock response in female mice

Murray K et al. (Oct 2020)
http://doi.org/10.1113/JP280518

The experience of exertional heat stroke (EHS) may increase risk of developing later-life health problems but the mechanism is unclear. This study used a mouse model of exertional heat stroke to investigate whether the stimulus produced a lasting epigenetic memory in monocytes and whether corresponding phenotypic alterations manifest. The model involved forced wheel-running at 37.5˚C/40% relative humidity (RH) until symptom limitation (characterised by CNS dysfunction). Results were compared with matched exercise controls at 22.5˚C. The authors found that DNA methylation was observed in promoter regions of genes associated with immune response in monocytes isolated from bone marrow 30 days post recovery. Following challenge with LPS, cytokine secretion (IL-6 and TNFα) was decreased compared with controls, suggesting impaired immune system function. Additionally, monocyte mRNA responded differently to a further heat shock challenge compared with controls. Rigorous exercise can suppress immune system function but this typically lasts 24 hours so is unlikely to explain effects observed at 30 days. Overall, given the responses observed, epigenetic remodelling leading to immunosuppressive effects may be a mechanism through which exertional heat stroke increases risk of other disease.

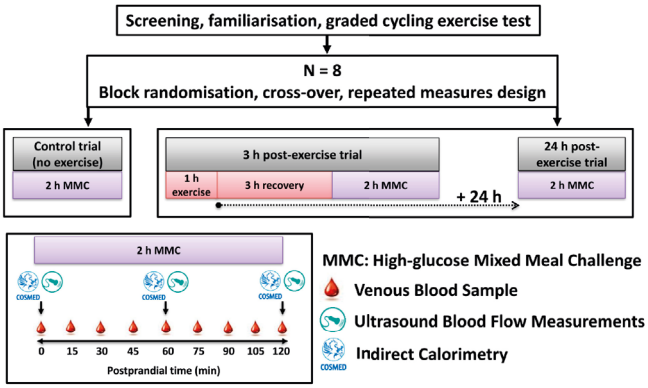


Schematic of the overall experimental design and distribution of samples. LPS = lipopolysaccharide. 42˚C exposure was the *ex vivo* heat shock challenge given to monocytes. Created by BioRender.com.

Prior exercise enhances skeletal muscle microvascular blood flow and mitigates microvascular flow impairments induced by a high-glucose mixed meal in healthy young men

Parker L et al. (Nov 2020)
http://doi.org/10.1113/JP280651

Impaired vascular function and peripheral blood flow have been linked to impaired substrate metabolism and are observed in states of insulin resistance including acute hyperglycaemia and hyperlipidaemia, and chronic cardiometabolic conditions including obesity and type 2 diabetes. High-glucose mixed nutrient meals decrease skeletal muscle microvascular blood flow. Exercise increases skeletal muscle microvascular blood flow. In this randomised cross-over trial, postprandial skeletal muscle microvascular blood flow was measured directly by contrast-enhanced ultrasound at different time periods following 1 hour of moderate intensity cycling (70–75% VO_2peak). The exercise stimulus was shown to increase postprandial (specifically, a high-glucose mixed nutrient meal) microvascular blood flow compared with no exercise in healthy young men. The effect remained up to 24 hours after the exercise stimulus. As diet and activity are cornerstones of human health, understanding how they interact builds towards strategies that may, for instance, be beneficial in conditions characterised by microvascular and glycaemic dysfunction.



Overview of the randomised crossover study design. Eight young healthy males ingested a high-glucose mixed nutrient meal at rest, and on a separate occasion at 3 h and 24 h after 1 h of moderate-intensity cycling exercise. Metabolic and vascular responses to the meal were measured throughout the postprandial period.

Simulated shift work during pregnancy does not impair progeny metabolic outcomes in sheep

Gatford KL et al. (Sep 2020)
http://doi.org/10.1113/JP280341

Perturbation of the circadian timing system around the time of birth may have later life health consequences. Given the global prevalence of shiftwork, which is associated with disrupted circadian rhythmicity, there is interest in whether shiftwork during pregnancy affects offspring health. Using a sheep model of simulated shiftwork (SSW; the indoor 12:12 light dark cycle was inverted twice per week) during either the initial third, initial two-thirds, or total duration of pregnancy, this study assessed metabolic outcomes in offspring at different age-points. SSW reduced birthweight for gestational age in singleton versus twin progeny but had no effect on postnatal growth. There were no differences in glucose tolerance

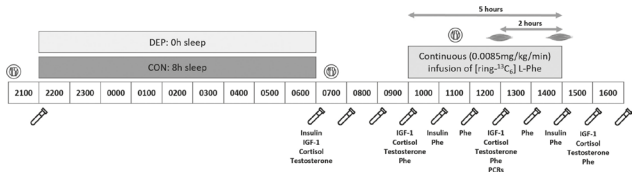
or insulin tolerance in pre-pubertal lambs (~100 days old). There were no differences in glucose tolerance at ~1 year in males but plasma insulin was lower between 30-60 min following glucose administration in females. There were no differences in insulin sensitivity at ~1 year in singleton progeny but some sex-dependent differential SSW effects were observed in progeny from greater litter sizes. No SSW effects on body composition were observed. Overall, the few observed SSW effects indicate improved metabolic health in sheep offspring. Differences in glucocorticoid secretion by pregnant mothers is postulated to explain differences in this sheep model compared to rodents. Shiftwork during pregnancy may affect health in human offspring.

Physiological Reports

The effect of acute sleep deprivation on skeletal muscle protein synthesis and the hormonal environment

Lamon S et al. (Jan 2021)
https://doi.org/10.14814/phy2.14660

Chronic sleep loss impairs whole-body homeostasis with profound effects on metabolism. This study sought to determine if one night of sleep restriction can affect postprandial muscle synthesis in 13 healthy young participants. Restricted sleep was maintained in the lab while control sleep was allowed in the home environment. Muscle biopsies were collected from healthy young participants following a night of sleep deprivation and normal sleep in a randomised crossover design. Sleep deprivation reduced muscle protein synthesis, increased plasma cortisol, and decreased plasma testosterone. There were no effects observed on plasma IGF1 (insulin-like growth factor 1), or core clock genes or protein degradation genes in muscle biopsies. Acute sleep deprivation may induce an acute anabolic resistant phenotype. These findings may be important in various settings and health conditions associated with sleep loss. The effects of acute sleep loss on metabolism and its contribution to health may be underestimated by many.



Experimental Protocol. Blood collection; muscle collection; standardized meal. IGF1, cortisol, and testosterone concentrations were measured at the 07:00, 10:00, 13:00, and 16:00 timepoints. Insulin concentrations were measured at the 07:00, 11:00, and 15:00 timepoints. Phe enrichment (Phe) was measured in both muscle tissue and blood samples between 10:00 and 16:00. PCRs were run on muscle tissue collected at 13:00

Experimental Physiology

Overexpression of Dnmt3a ameliorates diabetic muscle atrophy by modulating the Pten/Akt pathway

Wang M et al. (Sept 2020)
https://doi.org/10.1113/EP088894

Diabetes is amongst the most common pathologies globally, with a rapid increase in prevalence due to sedentary modern lifestyle behaviours and poor diet. As a consequence, diabetes-induced disturbances to our metabolic health lead to the development of a number of long-lasting complications that include damage to the muscles. In diabetes, muscle strength and functionality is diminished, greatly impeding an individual's quality of life. DNA ethyltransferases (DNMATs) are responsible, in part, for epigenetic control of gene expression. DNMAT3a has previously been demonstrated to preserve muscle health. Using a rodent model of diabetes that is induced chemically (using streptozotocin), this study demonstrated that DNMT3a expression is reduced in diabetes. Using a viral approach to overexpress DNMT3a delivered to the muscle in diabetic animals can return the expression of DNMT3a to normal levels. This rescue in DNMT3a expression prevented diabetes-induced muscle damage that was aligned to preservation of muscle tissue and induced expression of myogenic genes. This work highlights that regulation of DNA methylation via DNMT3a is inherently fundamental to muscle health and preventing its loss can prevent muscle damage seen in diabetics.

Synergistic effect of vascular endothelial growth factor gene inactivation in endothelial cells and skeletal myofibres on muscle enzyme activity, capillary supply and endurance exercise in mice

Sulaeman A et al. (Sept 2020)
https://doi.org/10.1113/EP088924

Healthy ageing is a fundamental research focus as our lifespans are extending due to ever-improving research technologies and healthcare systems. Unfortunately, despite this success in life longevity, an ever-increasing aged population is an economic and societal burden. With an ageing population comes increased susceptibility to chronic diseases that impact upon several physiological systems. This includes the vascular system and muscle physiology, which are heavily affected in several health-related complications. Typically, a decline in blood vessel number and reductions in blood tissue perfusion are attributable in part to the degeneration of the muscle, resulting in poor muscle coordination and strength. A protein known as Vascular Endothelial Growth Factor (VEGF), which is found in muscle and the endothelial cells that form blood vessels, is essential for maintaining vessel density in muscle tissues. Furthermore, in pathological states the expression of VEGF is diminished, impacting upon muscle tissue integrity. However, how VEGF and these differing cell types (muscle and endothelial cells) interact remain undefined. In this study the authors knocked out endogenous VEGF expression in endothelial and muscle cells, which resulted in a diminished capacity for mice to perform exercise, compared with wild type control littermates or mice that only had removal of VEGF from either skeletal muscle or endothelial cells. Despite these alterations in VEGF expression there was no impact upon blood vessel density; however, there was evidence of alterations in metabolic activity to compensate for the removal of endogenous VEGF expression.

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Meeting notes

GL Brown Prize Lecture: Healing Tiny Hearts Across Generations

3 December 2020
Held online

Nitika Gupta

University of Liverpool, UK

On 3 December 2020, The Physiological Society hosted this year's GL Brown Prize Lecture. The award honours the late Professor Sir Lindor Brown, who was a scientist known not only for his important contributions to the field of physiology, but also for his enthusiasm in encouraging and nurturing the next generation of scientific researchers.

This year's awardee was Professor Dino Giussani from the University of Cambridge, UK, who specialises in developmental cardiovascular physiology. As a PhD student investigating genetic cardiac diseases, I was excited to attend his talk, "Healing Tiny Hearts Across Generations"; I was particularly interested in learning more about the mechanism behind the programming of cardiovascular disease in a developing fetus, and the multi-generational consequences of this.

Professor Giussani and his group investigate the effects of exposure to hypoxia during foetal development on cardiovascular health in adulthood. Foetal hypoxia can be caused by common pregnancy complications such as pre-eclampsia and gestational diabetes (which affect 6% and 16% of pregnancies in the UK, respectively), and has been shown to lead to changes in the adult cardiovascular system that increase the risk of disease. According to the British Heart Foundation, 1 in 3 people in the UK suffer from some form of cardiovascular condition, so viable approaches to reduce the risk of predisposition to disease will have a great impact on the health of the general population.

Professor Giussani demonstrated how hypoxia in the later stages of pregnancy led to disease-associated phenotypes such as foetal growth restriction, increased mean arterial blood pressure and left ventricular hypertrophy. The underlying pathophysiology of these traits were shown to be linked to oxidative stress. Remarkably, these negative outcomes were significantly reversed by the administration of a mitochondrial-targeted antioxidant, MitoQ. The therapeutic potential of MitoQ or related drugs as an intervention to either prevent or limit the damaging effects of hypoxia at this crucial early stage of development could, therefore, have massive implications for the health of these individuals later in life.

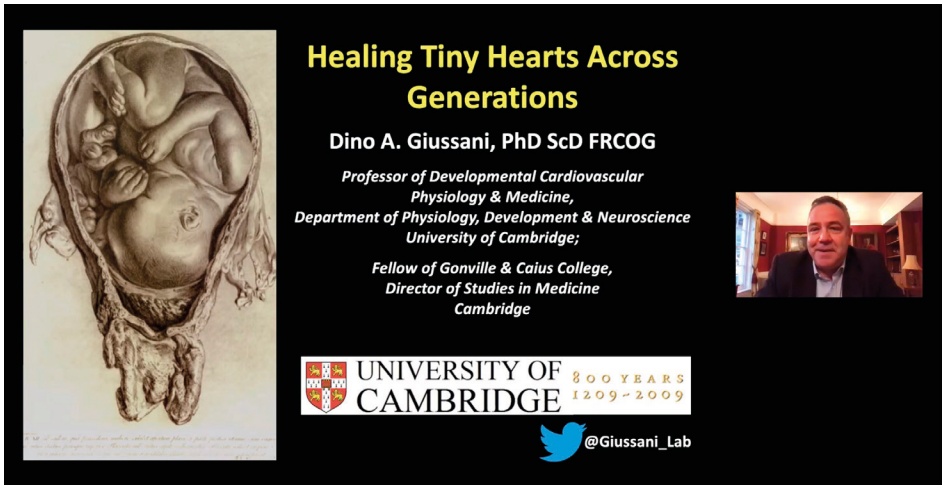
The second half of the lecture focused on the so-called "100-year effect," the idea that cardiovascular traits programmed in the developing fetus can be transmitted to subsequent generations. To investigate this, Professor Giussani's team isolated hearts from adult rats who experienced hypoxia *in utero* (F1 generation), and their offspring (F2 generation). By controlling the perfusion of these hearts, they were able to mimic and then measure the recovery from ischaemia, as an indicator of cardiac health. As predicted, F1 males displayed a slower recovery compared with those who were not exposed to foetal hypoxia. However, this slower recovery was also observed in F2 males with a paternal history of foetal hypoxia, suggesting a possible paternal inheritance of disease programming. In addition to this, Professor Giussani showed that cardioprotective traits mediated by mitochondrial function are developed in F1 males in response to foetal hypoxia, and are only passed down to the F2 generation via the maternal line.

These opposing patterns of either beneficial or detrimental trait transmission, possibly linked to epigenetic inheritance, raise many questions regarding the underlying mechanisms at play. For example, Professor Giussani found that the cardioprotective effect involved reduced protein kinase C-ε expression, which modulates mitochondrial processes and interacts with cardiac contractile machinery; this is also seen in ischaemic preconditioning. It would be interesting to see if there are further similarities or interaction with other cardioprotective mechanisms. I am also curious to see if F1 and F2 females demonstrated a similar pattern of trait inheritance, as there is research to suggest that female rodents have some inherent cardioprotection, due to factors such as differential K_{ATP} channel expression.

I really enjoyed listening to Professor Giussani's talk. As someone who uses primarily *in vitro* techniques, I learnt a lot about the uses of different animal *in vivo* and *ex vivo* models relevant to foetal development. But perhaps more importantly, following the journey of his research gave me a greater appreciation of the significance of multi-disciplinary collaboration to gain a more cohesive understanding, from molecular mechanism through to therapeutic intervention.

I'm sure the other attendees would have agreed with the chair, Professor Colin Sibley, who said that Professor Giussani's own invigorating personality, in addition to his academic work, made him a fitting recipient for this year's award. His warmth, good humour and enthusiasm for research was evident throughout the talk, as well as when responding to the sheer volume of questions submitted, many of which were from undergraduates. This really embodies the spirit of the GL Brown Prize in his desire and success in engaging young physiologists not only from the UK but also around the world.

Whilst it is uncertain when Professor Giussani will be able to share his lecture in person again (thank you, COVID-19), I look forward to hopefully meeting him in person in the future. In the meantime, I highly recommend watching his talk, which is available on YouTube **www.physoc.org/events/healing-tiny-hearts-across-generations/**, presenting innovative physiological research in a way that is more accessible to early career scientists and the wider global scientific community.



https://doi.org/10.36866/pn.121.33

Meeting notes

COVID-19 Conference: Lessons Learned from the Frontline

14 – 16 December 2020
Held online

Jacqueline Bennion

Therapy Services, Royal Free London NHS Foundation Trust, UK

In December 2020, The Physiological Society and the Intensive Care Society came together to host an exciting 3-day virtual conference focusing on the challenges of understanding the pathophysiological changes occurring throughout the body following COVID-19 infection. The conference shared current knowledge and thinking across many physiological systems, showcased the symbiotic relationship between physiology and critical care, and helped set the agenda for research to identify future treatments and therapies.

This conference, organised by Susan Deuchars, University of Leeds, UK, Steve Mathieu, Queen Alexandra Hospital, Portsmouth, UK, Mike Tipton, University of Portsmouth, UK and Hugh Montgomery, University College London, UK, was held just 1 year on from the early cases reported in Wuhan. It was unique in enabling the voices from physiology and intensive care to come together to discuss the challenges of identifying future therapies, the importance of rehabilitation and what questions remained unanswered. Both learned societies were delighted to bring together experts across disciplines to reflect on how we can progress our understanding of COVID-19, to improve outcomes in the future.

In 1952 a consultant anaesthetist Dr Bjorn Ibsen described what was the beginning of critical care medicine and the invention of manual positive-pressure ventilation during the polio epidemic in Copenhagen (Ibsen, 1954). And so, critical care was born, through a marriage of innovation between physiologists and clinical medicine during a tragic time in history.

The epidemic had resulted in daily local conferences to discuss lessons learnt. The effort developed collaborations between local anaesthetics, cardiologists, physiologists, nurses, physiotherapists, and ear, nose and throat surgeons. As a result, the diversity of critical care that makes it challenging to define was established.

Despite its youth, critical care has since produced innovation and multidisciplinary teams to improve the care of the most vulnerable and critically ill in society. Moreover it has built collaborative networks such as the International Forum for Acute Care Trialists to tackle equality in health education across global critical care units (InFACT). Over the course of just a few decades, it has evolved its focus from measuring patient survival to acknowledging the need for generalisable preventive and therapeutic interventions, in order to address the global burden of critical illness (Adhikari, Fowler *et al.*, 2010).

The COVID-19 pandemic has been, and still is, a painful and terribly sad time that will undoubtedly mark history. However, just as at the birth of critical care, there have been golden discoveries. From 14 – 16 December 2020, The Physiological Society, in collaboration with the Intensive Care Society, held a virtual conference featuring a sincere panel of experts. The panel represented a variety of areas of expertise such as genetics, virology, intensive care medicine, and exercise physiology.

The introduction of the conference reflected upon the challenges of COVID-19. Intensive

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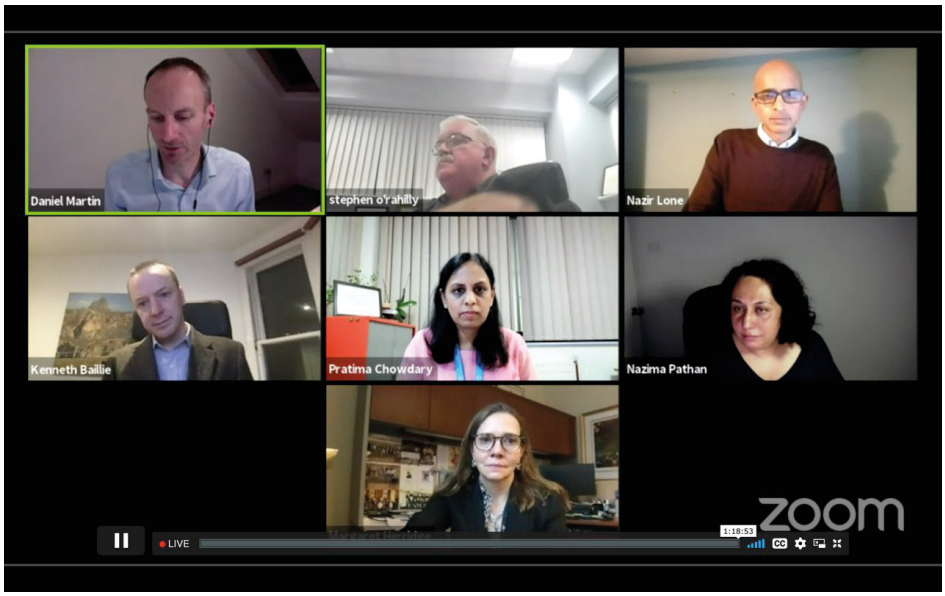


care consultant, Andre Vercueil, described the role of social media, and specifically WhatsApp, in drawing together anecdotal evidence between clinicians, physiologists and researchers to enable them to prepare, problem solve and learn. For example, he described how a professor from Italy WhatsApped a list of information about how to "get ready" for the COVID-19 virus, prior to its devastating arrival in the UK.

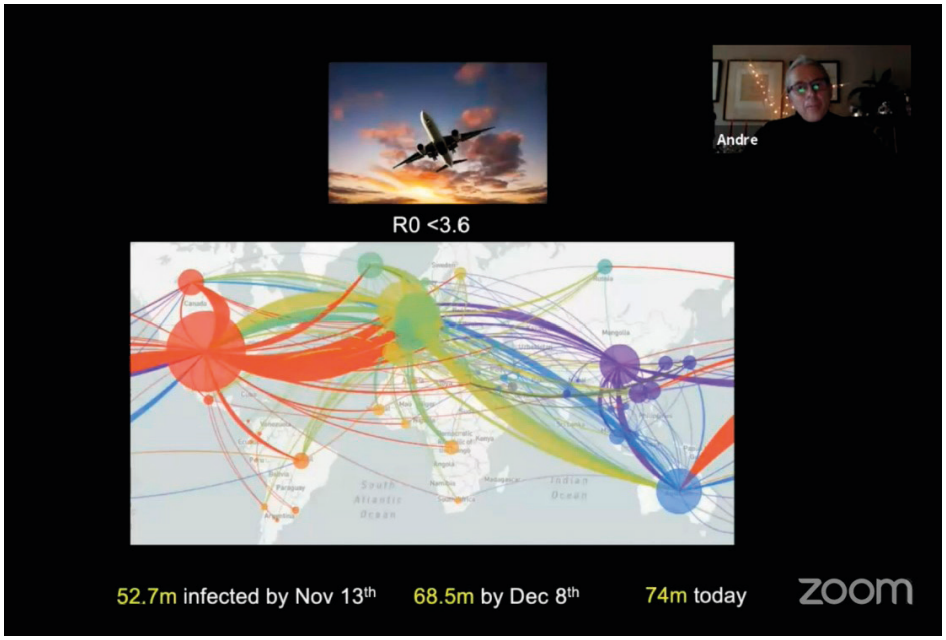
The conference eloquently communicated experiences, reflections, evidence, expertise and questions relating to the main human systems from micro to macro levels of physiology. The application of these equipped the critical care community to provide safe practice for critically ill patients, their families and relatives. The motivation of the conference, to ask questions and learn as a collaborative community, was demonstrated throughout, with open dialogue between novice and expert attendees, as well as with the expert panel.

Lessons I learnt included the role of clinical protocols, and the importance of a grounded physiological understanding in our response as clinicians. For example, intensivists and physiologists discussed the initial and current management of positive end expiratory pressures (PEEP) of mechanically-ventilated COVID-19 patients. This brought with it a discussion around the potential presence of physiologists in critical care.

Additional learning points included the increased number of physiotherapists carrying out rehabilitation in critical care and their role in patients' recovery from critical illness. We also discussed the complex role of science in governmental decision-making between public health and socioeconomic implications. Moreover, we reflected upon the observed grievous trends in the COVID-19 data suggesting social inequalities still very much exist in our UK society. To complete the conference, conversations centred on how conferences can host such an eclectic collaboration in the future to tackle current health issues. An expert panellist commented they had, "enjoyed making extensive notes and gathered more ideas from the collaborative discussions throughout this Physiological Society conference than they had for some time".

On reflection as a novice clinician and clinical researcher, the COVID-19 conference showcased the growth and development in innovation and care for the most vulnerable in society that has happened since the epidemic critical care was born. It demonstrated the unique and significant role of eclectic collaboration and confirmed that we all have a part to play, contributions to make, questions to ask, and so much to learn. Furthermore, the conference was a testament to the role of social media in developing knowledge sharing, diverse collaboration and innovation from a local position to what is now a shared global critical care community.

"The conference was a testament to the role of social media in developing knowledge sharing, diverse collaboration and innovation from a local position to what is now a shared global critical care community"



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InFACT International Forum for Acute Care Trialists. Promoting International Collaboration. Available: https://www.infactglobal.org/our-vision.

Meet the Early Career Theme Leads

Each Early Career Theme Lead represents one of The Society's seven Themes, together with their equivalent Theme Leads, as a coordinator of the topic area and the focal point for members, with a particular focus on early career researcher (ECR) engagement. They help promote the Theme activities and encourage members and non-members to participate in Society events and activities. Key roles and responsibilities include organising the annual Future Physiology conference, organising ECR networking, and developing opportunities for professional development.

Susan Deuchars
Chair of Conferences Committee (University of Leeds)

We are delighted to welcome these talented and passionate physiologists as our Early Career Theme Leads. Already, their energy and commitment is clear as they start to plan our next Future Physiology conference, with some innovative ideas for the programme. At The Physiological Society, we feel strongly that the input and opinions of our Early Career Researchers are of paramount importance in shaping the direction of The Society in all of our activities. They are the physiologists of the future and we are really appreciative of their efforts to ensure the continued vitality of The Society.

Daniel Brayson
Early Career Trustee (University College London)

In the realm of learned societies, The Physiological Society is pioneering in its willingness to experiment with the incorporation of early career scientists into leadership roles. The introduction of ECR Theme Leads will further enhance the relationship between ECRs and The Society. First impressions are that we have recruited an excellent cohort of bright, enthusiastic physiologists who will surely contribute to a stimulating, dynamic and fun culture at The Society.

Cardiac & Vascular Physiology

Greg Sutton
University of Edinburgh, UK

I am a fourth-year MRC Precision Medicine PhD student at the University of Edinburgh, UK. My main research interests are physiology, bioengineering, vascular biology and hypertension; however, my background is in infectious disease. I am also interested in teaching, networking, and enhancing academic engagement, particularly in under-represented groups.

I am proud to represent fellow early career cardiac and vascular physiologists at this important time. The Society, through its funding, conferences, and training events, has opened me up to new opportunities and helped me build new skills. I am looking forward to representing ECRs in The Society, looking for new ways for The Society to help with our professional progression and promote mentorship and greater engagement with early career physiologists.

Twitter: @endothelin1
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Education & Teaching

Ruth Norman
University of Leeds, UK

I am a teaching fellow in anatomy and physiology at the University of Leeds, UK and have been a member of The Physiological Society since the beginning of my PhD in 2012. My PhD was funded through teaching anatomy, which gave me invaluable experience alongside my research.

Having recently shifted focus from a cardiovascular field to more pedagogical interests, I have been impressed by the breadth of research and activities The Society provides. I have previously been involved with outreach events at past conferences and taken part in Physiology Friday. I believe ECRs from all areas in physiology can benefit from increasing their awareness and participation in education and teaching, which can provide rewarding experiences and skills for future careers.

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Endocrinology

Shelley Harris
University of Southampton, UK

I have a long-standing interest in endocrinology, particularly its role within integrated physiology. My PhD at Oxford Brookes University, UK focused on thyroid hormones and their role in perinatal growth. Following this, I was a postdoc at the University of Oxford investigating steroid hormones and their role in fatty liver disease. Currently, I am working in the Placenta Lab at the University of Southampton, using multi-scale imaging techniques to understand placental growth and structure.

During my PhD, I was the only student in the department with a physiology focus, specifically endocrinology. As a member I have always felt hugely supported by The Society from receiving travel grants, being given the opportunity to present my research at meetings and publishing my first ever paper. As ECR Theme Lead, I am enthusiastic about developing and promoting the support and activities that The Society can offer to ECRs working in the Endocrinology Theme.

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Epithelia & Membrane Transport

Jennifer Pearson-Farr
University of Southampton, UK

I am a postdoctoral researcher in reproductive medicine at the Department of Human Development and Health, University of Southampton, UK. My research is focused on the 3D architecture and function of the endometrial epithelium, the lining of the womb, and how it is related to pregnancy outcome.

I am very excited to be the Early Career Theme Lead for the Epithelia and Membrane Transport Theme. This Theme encompasses such a vibrant and exciting research area, which I am proud to be a part of. I am looking forward to becoming more involved in The Physiological Society community and I aspire to help support and shape the Theme in a way that keeps early career members in mind. I would also like to encourage engagement and outreach activities.

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Human, Exercise & Environmental Physiology

Paul Ansdell
Northumbria University, UK

I am currently a Lecturer in Exercise Physiology at Northumbria University, UK and recently completed my PhD studying sex differences in the integrative physiological responses to exercise. My research interests relate to diversity in physiological function, and how age, sex, and hormonal status influence acute and chronic responses to exercise.

The importance of physiology as a scientific discipline is becoming more and more evident, and I feel excited to be starting my career at a time like this. Undoubtedly, there are challenges facing ECRs currently, and in this role, I want to create opportunities for professional development whilst addressing those challenges. To do so, the other Early Career Research Theme Leads and I will be organising conferences, workshops, and other initiatives that promote the work of ECRs. Our collective aim is to enhance early career representation and participation within The Society.

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Metabolic Physiology

Kelly Bowden-Davies
Manchester Metropolitan University, UK

I am a Lecturer in Exercise Physiology at Manchester Metropolitan University, UK. My research is focused on the effects of physical (in)activity and sedentary behaviour on integrative metabolism, studying adipose tissue, skeletal muscle and the liver. Previous and current work examines how alterations in physical activity and diet affect metabolism in healthy individuals, those at risk of metabolic disease and patients with Type 2 diabetes. Given the rising prevalence of metabolic diseases, it is important to understand how lifestyle changes can reduce disease risk as well as its therapeutic role in disease management.

I am elated to join the Metabolic Physiology Theme as the Early Career Lead. I aim to work collaboratively across The Society and represent the needs of my peers as well as connecting junior and senior colleagues. I recognise that this period presents unique challenges and welcome any comments that could be used to support our community.

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Neuroscience

Laura Rich
University of Nottingham, UK

I graduated in 2016 from the University of Nottingham, UK with an honours degree in Neuroscience. During my degree I found my interest in glial cells and remained in Nottingham to undertake my Research Masters. I am still there now in the final year of my PhD investigating the metabolic interactions between neurons and glia in the central and peripheral nervous system.

Since attending Future Physiology 2017, my first conference, I have appreciated the support as an ECR from The Physiological Society, giving me the confidence to take on opportunities to engage further with The Society. (The professional development webinars certainly helped during the COVID-19 pandemic). I applied to become an ECR Theme Lead to contribute back to The Society and guide other ECRs along their scientific journey. I am looking forward to working with the other ECR Theme Leads and ECR members to develop the programme for Future Physiology 2021.

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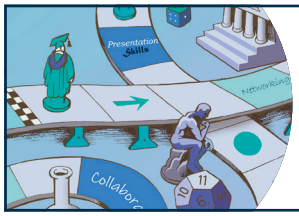

Future Physiology 2021 19 – 22 April

Future Physiology 2021 is organised by the Early Career Theme Leads. Registration is open and is free for all members (see page 18).

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A clinical perfusion scientist: The job and the role in ECMO during the COVID-19 pandemic

Naoise Ó Ciardha

Lead Clinical Perfusionist, Royal Infirmary of Edinburgh, UK

Kalynne Royds

Senior Clinical Perfusionist, Royal Brompton Hospital, London, UK

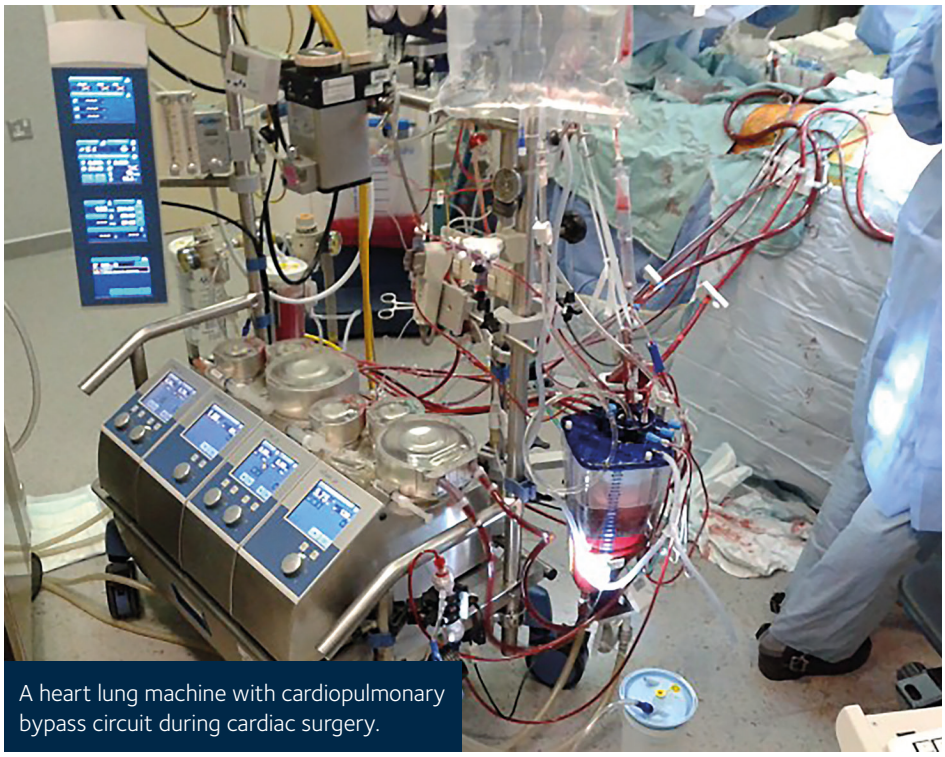
"Percussionist? Perfumist?"

Admittedly, the rhythmic pulsing of an ECG trace could sit comfortably alongside the timpani or xylophone but the scent of freshly cauterised fat against a backdrop of iodine and alcohol hand-gel is not something I would bottle. Once you get past the pronunciation, explaining the job of a perfusionist is slightly easier.

A perfusionist operates the heart and lung machine for patients undergoing cardiac surgery. Venous blood is drained from the right side of the heart via a large cannula into the cardiopulmonary bypass circuit of the heart and lung machine. Blood is pumped through an artificial lung called an oxygenator where gas exchange occurs. Oxygenated blood is then pumped into the ascending aorta to follow its normal course. The heart and the lungs are now isolated from circulation (i.e., cardiopulmonary bypass), providing a controlled environment for surgical intervention.

Indeed, opening the heart for valve repair or replacement requires it to be still. The perfusionist delivers a high potassium solution called cardioplegia to the coronary circulation, which causes an arrest – paradoxically, this same solution used for lethal injection protects the heart in this setting. Eliminating the heart's electrical activity and keeping it cool substantially reduces the metabolic rate of the myocardium, effectively putting it into a state of hibernation whilst ischaemic (Gay & Ebert, 1973). Once re-perfused with blood, resting membrane potential of the myocytes is restored and contraction can occur. This *Lazarus* moment of transition from a motionless mass to a dynamic organ is testament to the remarkable resilience of the heart.

During bypass, perfusionists must maintain haemodynamic stability, balance electrolytes through blood gas management, and monitor the coagulation status, all whilst ensuring the cardiopulmonary circuit is functioning correctly. An intricate knowledge of physiological processes is essential to manipulate the parameters of bypass to maximise not just O_2 delivery but whole-body homeostasis. For example, mimicking hypoxia by increasing the partial pressure of CO_2 can mitigate shunting of blood through aortopulmonary collateral vessels by causing them to constrict (Sakamoto *et al.*, 2004). Also, transient reductions in pump flow which impacts O_2 delivery can be tolerated if core body temperature is reduced (Cook, 1999).



A heart lung machine with cardiopulmonary bypass circuit during cardiac surgery.

Since the first successful use of cardiopulmonary bypass by Dr John Gibbon in 1953, extra-corporeal technology has evolved and become more refined, as has the profile of the person behind the pump. The perfusionist has shifted from an auxiliary to a highly specialised role with an MSc in Perfusion now required to practise in the UK and Ireland. Perfusionist roles also include coagulation management and blood conservation through the operation of cell salvage machines and point-of-care testing. With expertise in fluid dynamics, responsibilities also involve other forms of extracorporeal life support (ECLS) like ventricular assist devices and extracorporeal membrane oxygenation (ECMO).

ECMO is an advanced life-support that can be used in patients with cardiac and/or respiratory failure. The device is a miniaturised circuit capable of blood oxygenation, CO_2 removal, and haemodynamic support (Ali and Vutlsteke, 2019). Perfusionists are responsible for safe setup and deployment of ECMO, and maintenance and troubleshooting during use. Throughout the COVID-19 pandemic, ECMO has proven to be life-saving for many when conventional ventilatory intervention is not enough. SARS-CoV-2 can induce severe respiratory distress, subsequent failure of adequate blood oxygenation, and lead to global systemic hypoxia, hypercapnia, and organ failure. This can even occur despite invasive mechanical ventilatory support. ECLS has been essential in providing oxygenated blood to those with failing lungs. With ECMO, struggling lungs can recover without the risk of pressure-induced lung trauma from the ventilator.

The demand for ECLS has grown with the course of the pandemic. Specialised retrieval teams – comprising a critical care intensivist, a specialised nurse, and a perfusionist – have been mobilised to implement ECLS in severely affected patients and aid their transport to specialist hospitals with ECLS units, including the Royal Brompton Hospital in London. Currently, the ECLS unit at the

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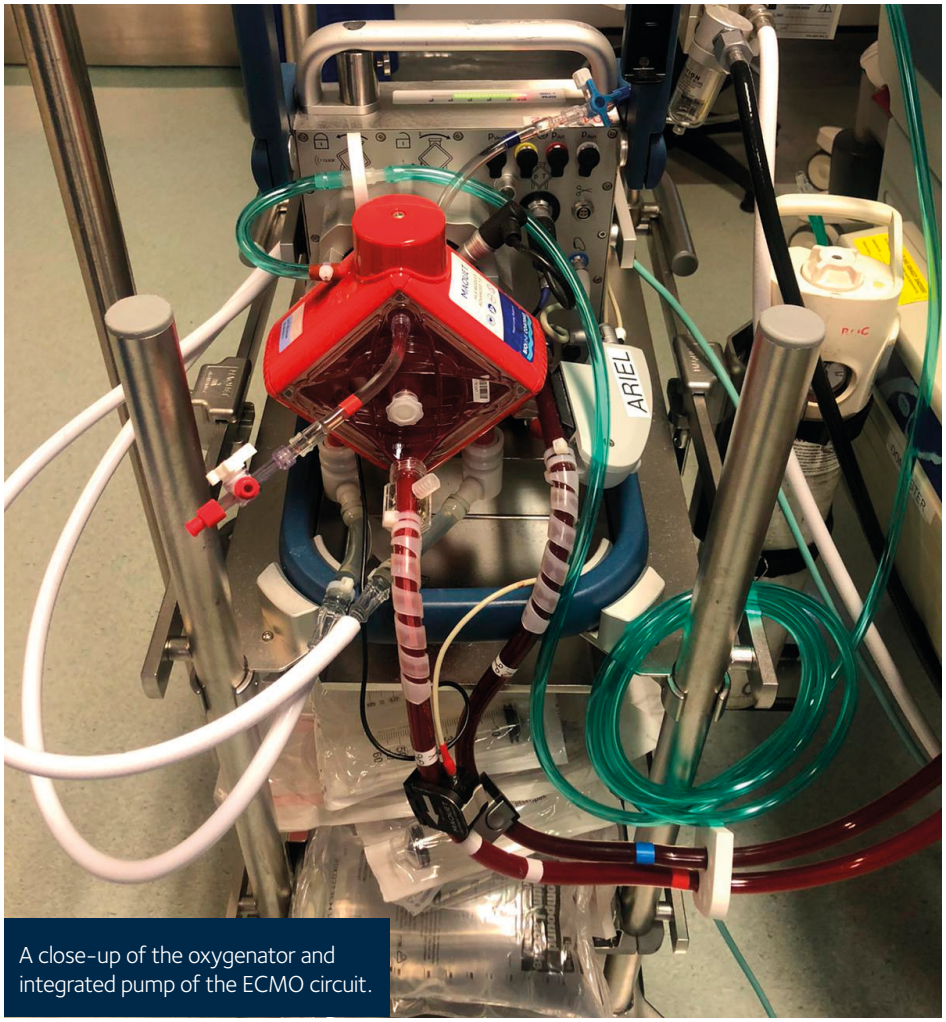
Royal Brompton can accommodate 25 ECMO-equipped beds. This is one of the largest units in England. While 25 may seem a small number, the number of staff and staffing hours required to provide round-the-clock care is high. Add in a year-long battle and a near permanent daily requirement of stifling personal protective equipment and it becomes a challenge of even greater proportion.

Unfortunately, the highly specialised and invasive nature of ECLS means supply does not meet current national or global demand and candidates must be screened for suitability. Furthermore, its implementation is not without significant risk to patients. Being artificial, anticoagulation of the patient's blood is necessary to prevent obstruction of the ECMO circuit; thus, imposing significant risk of bleeding. A delicate balancing act of preventing thrombosis and ensuring adequate haemostasis is required throughout ECLS intervention (Zhang and Zhou, 2021). Current data indicate mortality rates of up to 38% for COVID-19 patients in the 90 days post-ECLS intervention (Barbaro *et al.*, 2020). One of the primary concerns when considering a suitable candidate is the reversibility of their pathological state and their ability to regain physiological independence when removed from the ECMO circuit.

The greatest burden to the ECLS team during the pandemic is deciding who is and who isn't a candidate for ECMO. However, the decisions surrounding implementation of ECLS and best patient care has encouraged discussion amongst multidisciplinary teams and boosted medical ingenuity and quick progress in COVID-19 treatment modalities.

A patient on ECMO in the intensive care unit at the Royal Brompton Hospital.



A close-up of the oxygenator and integrated pump of the ECMO circuit.

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Applied physiology in the COVID-19 pandemic: Measurements on the frontline

Brendan Cooper

President, Academy for Healthcare Science, University Hospitals Birmingham NHS Foundation Trust

Within the National Health Service (NHS), clinical physiologists contribute an enormous amount to routine clinical services and are based both in out-patient and in-patient roles. There are at least eleven professions in physiology delivering a wide range of physiological techniques: audiology, autonomic neurovascular function, cardiac physiology, clinical perfusion science, critical care science, gastrointestinal physiology, neurophysiology, ophthalmic and vision science, respiratory and sleep physiology, urodynamic science and vascular science.

Traditionally, clinical physiologists or scientists performed mainly diagnostics, but in recent decades, roles have evolved into delivering interventions and treatments, often including monitoring, across the spectrum of professional specialisms. These services can take place in venues as diverse as the patient's home, operating theatres, critical care units and hospital wards. Variety, flexibility, and varied complexity are common themes across all clinical physiology roles.

Clinical physiologists generally use techniques that measure pressure, flow, volume, electrophysiological activity, or imaging, to support clinical diagnostics. There are training pathways in most of the professions, which are part of the national training programmes run by the National School for Healthcare Science (NSHCS), or professional body programmes. All training programmes have theoretical and practical components, and courses ensure that practitioners understand not only the physiological principles but achieve clinical competence in appropriate techniques (Fig. 1). Entry level for graduates at Bachelor's, Master's or doctoral level is possible, with the Master's level Scientific Training programme (STP) being the most popular option for graduates. These training courses are often themed in groups of physiological specialities (e.g. cardiac, respiratory and vascular).

Clinical physiologists and scientists often work directly with patients to measure and monitor particular conditions, using their knowledge and competencies in physiological systems, such as:

- Carrying out echocardiograms to check how the heart is working;
- Undertaking diagnostic tests of flow, pressure, and volume to assess lung function;
- Measuring eye function and taking images of the eye and its supporting structures;
- Assessing hearing and balance function in everyone from babies to the elderly;
- Investigating the nervous system to diagnose and monitor things like epilepsy and multiple sclerosis;
- Diagnosing and treating patients with sleep problems such as sleep apnoea, where people temporarily stop breathing.

Clinical physiologists are very much applied physiologists, and it is interesting to examine a typical diagnostic test that incorporates the applied physiology that is essential on the frontline of the NHS. In respiratory and cardiac physiology, the cardiopulmonary exercise test (CPET) is regarded as the "gold standard" to evaluate the limitations ofphysiological performance of the body in health and disease. One reason for this is that the physiological and metabolic stress of surgery is related directly to the ability to perform beyond a threshold of exercise ability. Indeed, patients who fail (so to speak) such pre-operative CPET tests often require more critical care and have higher mortality than those who pass the threshold.

"Scientists are very good at quickly retraining and adopting new roles in a controlled and consistent manner"

CPET essentially requires the subject to breathe through a flow-measuring device (e.g. pneumotachometer, ultrasonic flowmeter, hot-wire anemometer, mass flow meter) and the signal is integrated to produce volume as well as measuring respiratory rate. From these signals, minute ventilation, tidal volume, and other subdivisions of volumes and capacities are calculated. Expired gas analysis using oxygen cells and infrared gas analysers, together with the volume signal, calculate oxygen uptake, carbon dioxide production and other calculated values from these. In addition, the electrocardiogram is used to monitor the electrophysiology of the heart, but also to calculate heart rate and oxygen pulse, which is an estimate of stroke volume utilising rearrangement of the Fick equation ($CO = VO_2/(Ca - Cv)$. This is classic physiology utilised in direct patient measurement!

Pulse oximetry is essential to monitor oxygen trends during the test, and quite often an arterial or "arterialised" blood gas can be used to measure blood-gas status and derive the ratio of dead-space to tidal volume (V_D/V_T) or the alveolar–arterial difference as an assessment of gas exchange.

Of course, all these physiological methods require calibration of equipment, validation of signal quality and are usually part of an overall quality control scheme in physiology departments. In recent years accreditation of NHS physiological services has meant that several centres now have UK Accreditation Service (UKAS) compliance as part of the scheme called Improving Quality in Physiological Service (IQIPS). This means that patients are protected by not just safe measurement, but safe and reliable processes from their appointment to the final report.

There are many other examples of the use of applied physiology in any of the physiological professions listed above. For physiology graduates, a career as a physiologist in the NHS is not just rewarding, but one of the most interesting and varied careers for scientists in the NHS (in my biased opinion, of course!). This has been exemplified recently by the deployment of physiologists to support the front line of the COVID-19 pandemic.

The COVID-19 pandemic has changed the role of healthcare physiologists and their standing within hospitals and healthcare across the UK in an unimaginable way. Whilst many of the routine services delivered daily

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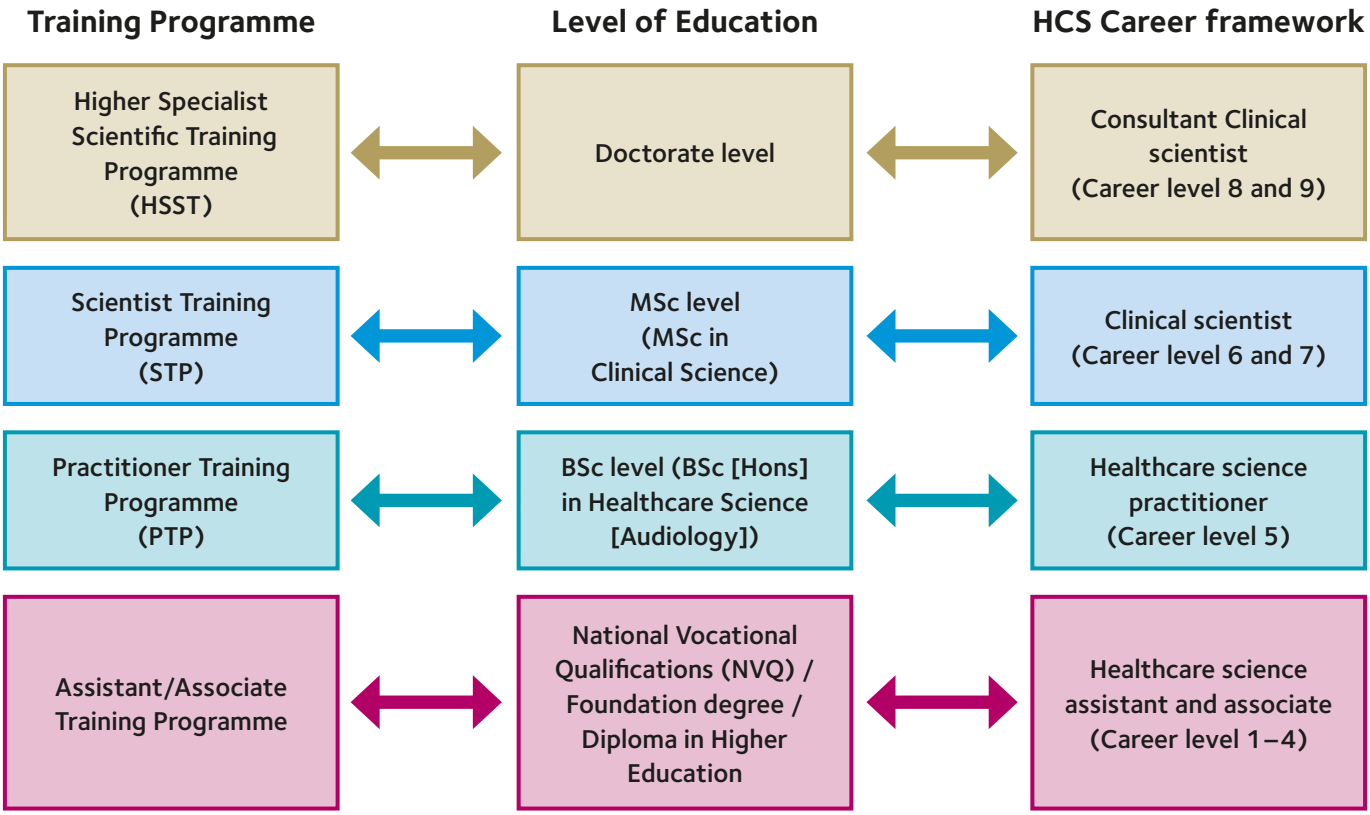

Figure 1. Training pathways and structures for UK Healthcare Scientists showing the training programme, level of education and career framework. This is applicable to most physiological healthcare sciences.

have scaled back, clinical physiologists have been on wards and in critical care delivering their usual essential services, often in full PPE, but under very stressful situations. Furthermore, because of their clinical skills with meeting, handling and caring for patients, they have also been deployed to support on wards acting sometimes in a healthcare assistant role - taking regular observations (temperature, blood pressure breathing and heart rates), assisting with patient direct care (bedpans/commodes!) and talking with patients who are often scared, lonely and anxious. This utilises the "care" part of being a healthcare scientist and makes the role more fulfilling, as well as occasionally exhausting.

Respiratory physiologists have been used on COVID-19 wards to support continuous positive airways pressure (CPAP) and high flow nasal oxygen (HFNO) in some very sick patients, often working overnight, at weekends and/or long shifts. Ventilators are often used clinically in accordance with clinically agreed protocols, but having an understanding of the underlying physiology – lung compliance, airflow, gas exchange, response times, physiological variation, all contribute to gaining confidence and understanding at the bedside. Sometimes you may have the opportunity to teach nurses or junior doctors about the physiology of the ventilation, the physiology of coronavirus or the reasons why a particular probe is not working.

Many physiologists (from all professions including audiology, neurophysiology, GI physiology etc.) and at different grades from juniors to consultant clinical scientist level, have been redeployed to support critical care teams looking after intubated, ventilated patients. Others have assisted with infection protection and control by ensuring all clinical staff going on to wards or ITU use the correct personal protective equipment (PPE) procedures during "donning and doffing" of protective equipment. Scientists are very good at quickly retraining and adopting new roles in a controlled and consistent manner – perhaps something learnt in the methodical scientific approach to their work on a daily basis. No task is too menial in this COVID-19 emergency.

I hope there are some physiology graduates and postgraduates reading this, who feel they may want to work in a more clinical patient-facing role, or even expand their research from the bench to the bedside, and may be inspired to become clinical physiologists or scientists. There are often many vacancies and sometimes niche ways of joining the profession as well as coming through the training programmes listed above. Often hospitals will offer in-service training programmes or apprenticeships for graduates (e.g. sports science graduates often get trained in respiratory and cardiac physiology departments).

To study physiology and then spend your career delivering applied physiology and conducting physiological research is an enormous privilege. And to be on the frontline of the NHS during this pandemic and help patients is an absolute honour!

Further reading

National School of Healthcare Science
https://nshcs.hee.nhs.uk/

Academy for Healthcare Science
https://www.ahcs.ac.uk/

Four Nations' Chief Scientific Officer Offices:

England **https://www.england.nhs.uk/healthcare-science/cso-programmes/**

Wales **https://gov.wales/dr-rob-orford**

Scotland **https://www.gov.scot/policies/health-workforce/healthcare-scientists/**

Northern Ireland **https://www.nidirect.gov.uk/articles/healthcare-scientist**

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Lab profile: The Centre for Renal Tubular Physiology, University College London

Stephen Walsh

University College London, UK

The renal physiology laboratory was set up at the Royal Free Campus of University College London (UCL) by Professor Robert Unwin in 2001. Although Professor Unwin was trained in micropuncture at Yale, and he published widely in animal models of disease, his interest was always in patients.

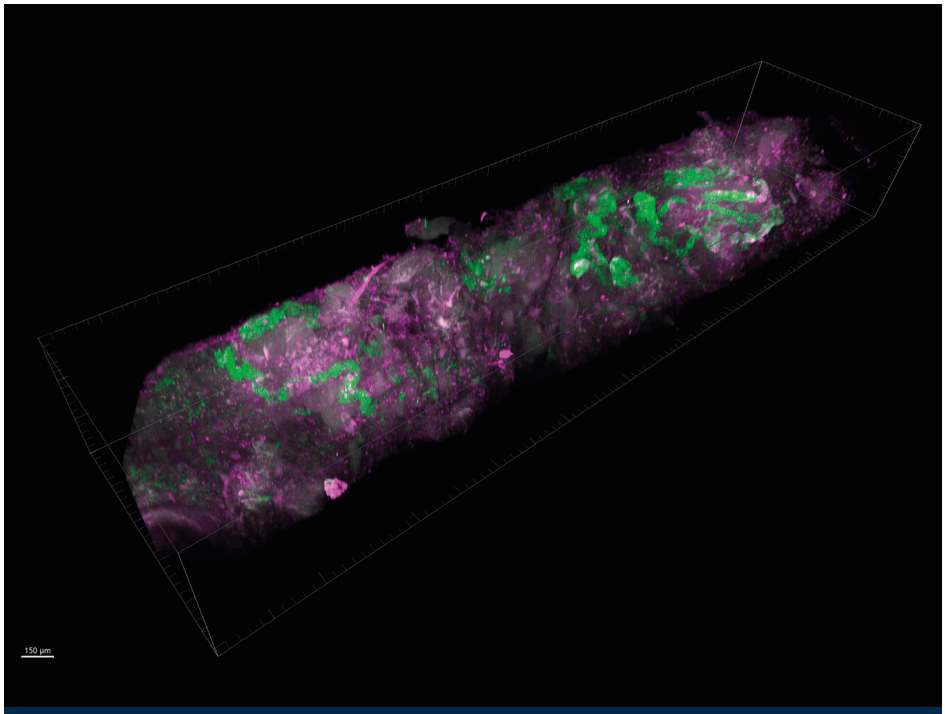
Now I head the centre, and while we do some animal work to unpick the underlying fundamental physiological processes, our focus is really on humans and specifically human renal tubular physiology. Our special interest is in disorders of sodium transport, blood pressure homeostasis, and the distal convoluted tubule (DCT).

The bedrock of the centre is the UCL Tubular Clinic, where we see patients with very rare renal tubular disorders, both inherited and acquired. We look after the largest cohorts of patients with Gitelman and Bartter syndrome in the UK, as well as large cohorts of patients with Gordon syndrome, distal renal tubular acidosis, the renal Fanconi syndrome, and other rarer electrolyte and acid–base disorders. We get referrals from all over the UK, importantly including our sister clinic at Great Ormond Street Hospital, as well as frequent calls for remote advice. We offer specialist diagnostics (specialist biochemistry, genetics and physiological testing) and therapeutics (including specialist supplements and immunomodulatory treatments).

"The bedrock of the centre is the UCL Tubular Clinic, where we see patients with very rare renal tubular disorders, both inherited and acquired"

Renal tubular physiology is also very important to consider in patients who develop either kidney stones or hypertension. We have a specialist metabolic stone clinic to diagnose rare disease causes of kidney stone formation. We also set up a Complex Hypertension Clinic, where we screen patients with unusual or treatment-resistant hypertension for rare secondary causes of hypertension, and for evidence of poor patient compliance (i.e. flushing their pills down the drain!).

The rare disease patients also contribute to research; we conduct genetic studies for novel gene discovery (EAST syndrome, for example, was discovered here), carry out imaging studies of the hearts of Gitelman and Gordon syndrome patients and measure the urinary excretion of salts and exosomes in these patients when they are exposed to diuretics and other pharmacological agents. This is work that is being done by one of our clinical research training fellows, Dr Beth Wan.



3D image of an intact human kidney biopsy. SHIELD samples can undergo multiple rounds of multiplexed labelling of clinically useful stains (green - LEL lectin labelling of distal tubules / magenta = 555 nm autofluorescence).

This unusually dense collection of very rare human disease means that we have access to both patients and human biosamples, which have allowed Dr Keith Siew, a Sir Henry Wellcome Postdoctoral Fellow in the Centre training in micropuncture and imaging, to translate his findings from animal models to humans.

We have advanced imaging facilities and use modern optical clearing techniques to render human kidney tissue transparent (the methodology we use is called SHIELD). We then probe them with oligonucleotides, antibodies and/or stains and image them, using light sheet microscopy in 3D. We are developing this for rare disease basic research, comparative physiology, and new human diagnostic techniques, along with our consultant histopathologist, Dr Lauren Heptinstall, who is one of the researchers in the centre.

The centre was well known for the difficult micropuncture and microperfusion techniques that were pioneered at Yale. Anatomical limitations mean that distal nephron physiology is almost impossible

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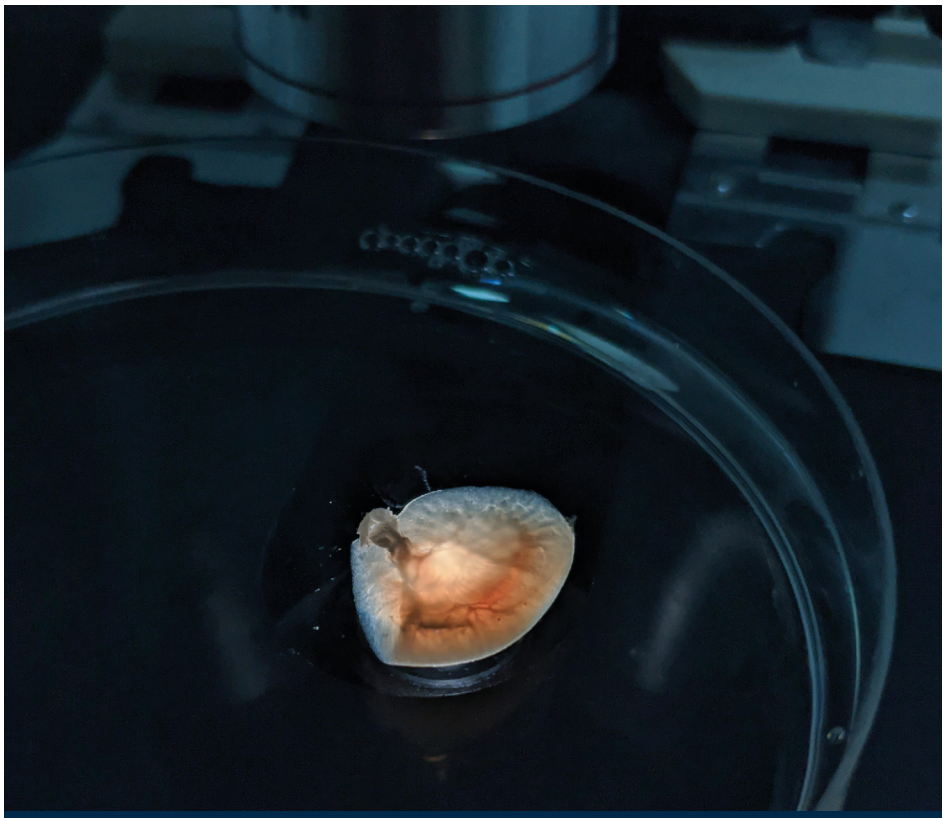
to study using micropuncture in mice, and although humans are the right size for this, we have not yet managed to convince an ethics committee to let us try.

The clumsily named organ-on-a-chip technologies offer a way out of this ethical conundrum. We have immortalised human DCT cells and are able to culture them in 3D tubular cultures with directional luminal flow. Furthermore, we have been able to isolate and culture DCT cells from rather large volumes of human urine. Growing 3D cultures of primary human DCT cells is the next step and offers exciting new possibilities for physiology and diagnostics. This work forms part of the training for Eunice Zhong, one of our PhD students.

The centre has full cell biology, proteomic and bioinformatic capabilities and is rapidly developing the hardware and computer scientists to analyse the complex and dense data generated by these new techniques.

The geeky tech obsession that permeates the centre carries over into the lab meetings, which are conducted on a number of fashionable web-based apps (depending on the whims of Drs Walsh and Siew), in addition to the standard video conferencing apps so prevalent in COVID-19 times.



Hemisected SHIELD-treated rat kidney after delipidation: To optically clear tissues, we use formaldehyde and epoxy resin to form a hydrogel–tissue hybrid (SHIELD) and then strip away lipids with SDS.

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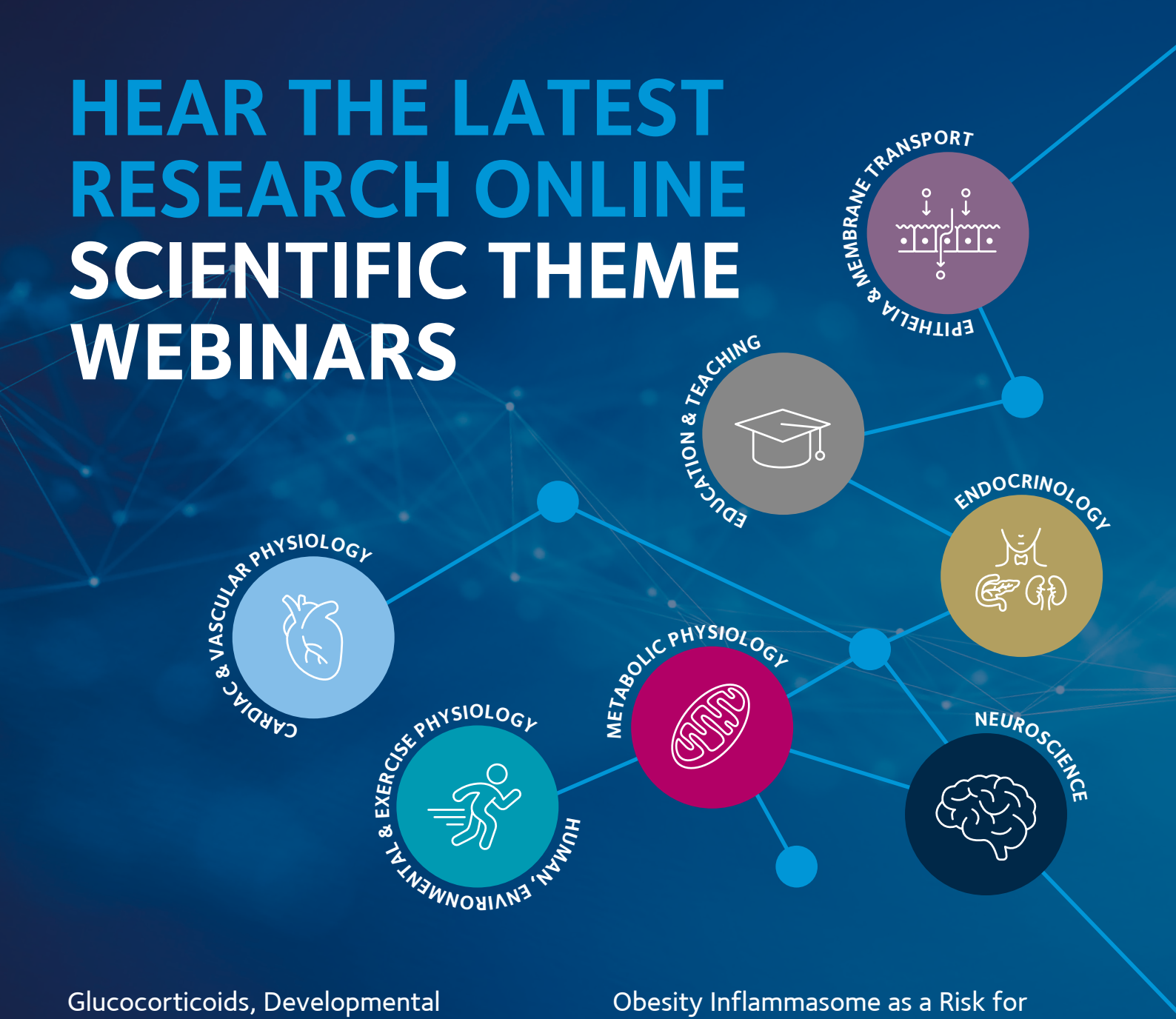

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Obituary: Otto F Hutter 1924 – 2020

Otto F Hutter

Honorary Member Otto Hutter died peacefully, aged 96, on 22 November 2020 at his home in Bournemouth. First elected to The Society in 1953, he was the then longest serving member.

Otto's research work focused on nerve and muscle electrophysiology. His reputation was established early when, with Wolfgang Trautwein, he first revealed the electrical changes responsible for the slowing and speeding of cardiac pacemaker rate by vagal or sympathetic innervation (Fig.1). His parallel enthusiasm for, and innovations in, teaching were recognised by The Society naming its annual teaching prize, the Otto Hutter Physiology Teaching Prize, in his honour.

Otto was born to a Jewish family on 29 February 1924 in Leopoldstadt, central Vienna. His happy childhood included attending the Zwi Perez Chajes *Gymnasium*. However, the *Anschluss*, the annexation of Austria by Nazi Germany in March 1938, signalled shattering changes. When just 14, a chance meeting with a friend on the Marienbrücke over the Danube Canal near his home encouraged him to register for the *Kindertransport* evacuation. He became number 359 of the 360 children on the train that left in December 1938, despite his having no familial or personal connections in the UK. Otto retained that *Kind 359* ticket all his life.

From December 1938, Otto was fostered by the Blaxill family in Colchester. Letters from his father reinforced his aspiration for a strong education rather than "learning a trade", otherwise typical at age 14. He secured one of just two refugee scholarships generously sponsored by the Old Boys Association of Bishop's Stortford College, opting for the Science Sixth Form. In 1942, considering himself "not robust enough" for the Pioneer Corps, the only option for a refugee, he took up "essential war work" at the Wellcome Physiological Research Lab (WPRL) in Beckenham, south-east London. There he worked on standardising insulin and testing penicillin for pyrogen. He was able to continue science studies on evenings and weekends at the then Chelsea Polytechnic and Birkbeck College. He also attended a lecture course called Chemical Transmission in the Nervous System given by Sir Henry Dale at the Royal Institution. Whilst at WPRL, he met Yvonne who was to become his wife of 70 years.

At the end of the Second World War, the grim truth of the loss of almost all his family became clear. Just from Otto's home street, Lilienbrunngasse in Vienna, some 493 Jewish men, women, and children had died in the Holocaust.

From 1946, Otto took the BSc Honours Physiology course at University College London (UCL), followed by a Sharpey PhD Fellowship there under Sir Charles Lovatt Evans (remembered in the *Physiology News* article Otto completed just before his death: Hutter, 2020). Lovatt Evans' lecture-demonstration teaching method was to prove a major influence on Otto.

Otto's early research investigated tetanus toxin on neuromuscular transmission. During these experiments, a cat nipped his fingertip. Weeks later a threatening adenopathy developed in one arm. It resisted the antibiotics then available, but eventually yielded miraculously to massive doses of potassium iodide, an ancient last-ditch remedy.

Otto was then appointed Lecturer at UCL. A 2-year Rockefeller Travelling Fellowship at Stephen Kuffler's lab at Johns Hopkins University in Baltimore began in 1953. He worked initially with another visitor, Werner Loewenstein. He met Otto Loewi at Woods Hole, recalling that "when animated, as [Loewi] often was, he spoke in a mixture of Austro-German and English which I could comprehend well enough". Loewi's suggestion that Otto should read Gaskell's work from the 1880s on the tortoise heart was pivotal.

His work with another visitor, Wolfgang Trautwein from Heidelberg, was iconic. In what most would consider very early microelectrode work (Bretag, 2017), they studied the cardiac pacemaker potential in frog and tortoise hearts. (At that time microelectrodes were hand-pulled from capillary glass over a Bunsen burner and much of the necessary electronic equipment was constructed by the experimenters themselves). Hutter and Trautwein revealed the pacemaker potential slowing and speeding under the influence of vagal or sympathetic nerve stimulation, respectively (as well as by the neurotransmitters those nerves release).

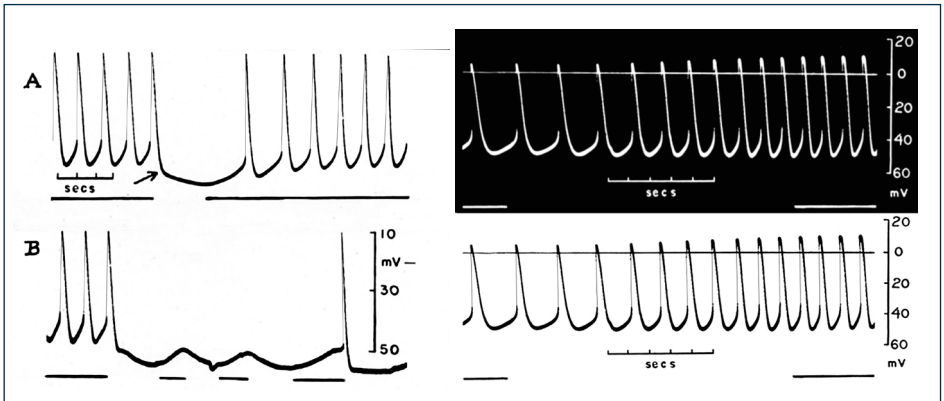

Figure 1. Two key figures from Hutter & Trautwein, 1956: see original paper for detail. Reversed black/white from originals, "rising phases slightly retouched". *Left:* The rate of firing of action potentials (APs) of frog sinus venosus pacemaker cells is slowed or even stopped, by stimulation of the vagus nerve (gaps in line below trace). Repolarisation is faster and "diastolic" membrane potential is more negative during vagal stimulation. *Right:* Original above, revised version below. Rate of firing is increased by stimulating the sympathetic supply (gap in line below trace). APs rise and fall more steeply, AP peak is higher and diastolic potential more negative than control. (Atropine present to block vagal effects).

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The Hutter lab, Glasgow, 1980.

Otto Hutter during Oral History interview, Tilli Tansey's office, 1996.

The inability of the camera system to capture the fast-rising phase of action potentials reinforces the experimental challenges of the time (see Fig. 1). But the images they secured now grace virtually every medical and physiological textbook – albeit too often in near-cartoon versions.

Otto's subsequent studies (back at UCL) of the underlying mechanisms furthered his interest in potassium and anion conductance channel properties, notably in skeletal muscle, expanding this field considerably. His students there were SM Padsha and Denis Noble. A key finding was of the substantial chloride conductance of skeletal fibres; their outward rectification and the inward rectification of K^+ conductance were successfully quantified. The much lower Cl^- conductance of cardiac muscle was also revealed: the rank order of foreign anion permeability in cardiac muscle proved to be the reverse of that in skeletal muscle. In 1961, Otto transferred to Wilhelm Feldberg's Division at the MRC's National Research Institute in Mill Hill: Anne Warner was his PhD student. Here he continued studying actions of various anions, formaldehyde and pH on sarcolemmal K^+ and Cl^- conductances.

In 1971 Otto fulfilled his wish to return to academia when appointed Regius Professor of Physiology at Glasgow University. His research moved on, studying the Graafian follicle (with Colin McCaig), adenosine actions on the sinus venosus (with Andy Rankin), deploying techniques of noise analysis and patch clamp (with Tom DeCoursey, John Dempster, Francis Burton). Computer-based data acquisition and analysis were introduced early to support his work and that of others in his department. In later years at Glasgow, he returned to simpler experiments on sarcolemmal vesicles in work relevant to muscular dystrophy (with Francis Burton, Jim Nichol, Douglas Bovell), yielding information on mechanical properties and water permeability. Otto sustained his deep scholarship of Cl^- and K^+ conductances, giving a masterly review of the topic to a spell-bound audience of early career researchers at the 2016 Physiological Society annual conference in Dublin (Hutter, 2017).

In parallel with his research, around 1966 Otto persuaded The Society to support practically orientated short courses for school teachers, marking the beginnings of The Society's Education Subcommittee. He also became involved with the International Union of Physiological Sciences (IUPS), first as Commission Chairman and then on its Council. During a 12-year stint, he pioneered the Educational Workshops that became a feature of IUPS Congresses. He also convened special workshops in (then) developing countries, such as a patch-clamp workshop at the Shanghai Institute of Physiology in 1983, led by Dick Tsien. The Society's *Otto Hutter Physiology Teaching Prize*, founded in 2009, recognised these endeavours.

"Those fortunate enough to experience his small-group teaching remember being challenged but greatly enthused"

Otto was a gifted and dedicated teacher, taking that aspect of professorship seriously. Lecturing to 250 medical or science students demands a major performance. He would remark, "If you're not nervous before a lecture, you're not taking it seriously enough!". Those fortunate enough to experience his small-group teaching remember being challenged but greatly enthused. He pioneered the use of sophisticated instrumentation for large junior labs. In the mid 1970s, a set of 32 identical, oscilloscope-based workstations were resourced, designed and constructed (Eadie *et al.*, 1974). Thus, lab groups of 32 student pairs could simultaneously complete hands-on work in core physiology practicals, enabling several hundred medical, science and dental students to learn by doing each week. Then, in the mid 1980s, the system was replaced in an early move to computerisation, deploying so-called BBC micro-based workstations (Edmondson *et al.*, 1987; Orchardson *et al.*, 1989). Well-equipped and -staffed departmental electrical and mechanical workshops were supported by his advocacy, vital both for research and for teaching with a substantial practical content.

After retirement, Otto continued to publish reviews and opinion pieces, often with letters in *The Times* on science or Israel's politics. He had sustained his love of gardening at a flat at Kilchattan Bay, Isle of Bute. Soon after the millennium, he and Yvonne moved to Bournemouth to be nearer to family, to continue gardening and to give talks on bioscience topics to lay audiences. His scholarship of Judaism grew further. His identity as a Holocaust survivor became more prominent: he gave several lectures and attended reunions. In 1996 he was interviewed for The Society's Oral History series (see Hutter, Tansey and Rosenberg, 1996). In 2001, with Bernard Wasserstein

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at Glasgow University, Otto established the prestigious Annual Holocaust Memorial Lecture series. Remarkably, at the age of 94, he gave the 18th lecture himself to a sell-out audience (Hutter, 2018). He had meticulously researched the varied careers, or sad fates, of nearly all his 37 school classmates from 1938. He sustained a large network of correspondents to the end. By the time of his death, he had family in the UK, Israel and Australia with 27 great-grandchildren. Otto became an Israeli citizen in 2018.

Professionally, Otto was first and foremost a gifted scientist. He had enormous powers of concentration and dedication to envisage and execute complex experimental work and then to conduct the thorough analysis of the data that followed. The authors, as well as many others fortunate enough to have known him, now retain fond memories of: the sheer energy he always had; his lively mind; the joy he took in helping those less gifted to understand; his attention to details; his enthusiasm; the pleasure he took in whatever he was attending to, be it world-class science or his garden; his deep love and pride in his family; his respect for his Jewish heritage; his wide scholarship; the lively twinkle that never left his eye; the ready smile; the charming anecdote; and his impeccable memory for facts, names and faces.

Otto was fond of quoting the Talmudic sages. His life and work surely fulfilled the counsel of Rabbi Tarphon: "You are not required to complete the task, but neither are you free to desist from it".

Otto Hutter was elected to The Society in 1953, Honorary Member, 1991, served on the Editorial Board of The Journal of Physiology (1961–1966), The Society Committee (1968–1972).

Written by David Miller, University of Glasgow, UK, and Denis Noble, University of Oxford, UK.

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Obituary: Jan Lännergren 1939 – 2020

Jan Lännergren

Jan Lännergren grew up in Stockholm and completed his medical training at the Karolinska Institutet, Sweden. After compulsory military service as a medical officer, he returned to the Karolinska Institutet and in 1967 he presented his PhD thesis entitled "Mechanical activity of twitch and slow muscle fiber in *Xenopus laevis*" with Bernhard Frankenhaeuser as his supervisor. Aside from sabbaticals with Andrew F Huxley at University College London, UK, with Russel Close at the Australian National University, Canberra, and with Willem van der Laarse at Free University Amsterdam, Netherlands, Jan spent the majority of his career at the Karolinska Institutet, where he became a Professor of Physiology in 2000.

Jan was a perfectionist in his approach to research. Fuelled by strong freshly brewed coffee and a pipe, later replaced by nicotine chewing gum, he spent weeks refining muscle fibre dissection and recording chambers, stimulators, and amplifiers. His designs, albeit highly complex, turned out to be infinitely robust and some of his muscle chambers and stimulators are still in use more than 30 years after they were built. His constant search for perfection ensured that the experiments performed were of the highest quality, but the downside was that this slowed his research output. Thus, his major results remain valid and are still quoted. Luckily, this was before the modern era where the presumed importance of data is assessed by extensive, and sometimes irrelevant, statistical analyses.

Jan's work is influential in that he demonstrated the feasibility of using mechanically dissected, single, intact muscle fibres from amphibians and mammals to address fundamental physiological questions. An early research interest of his was properties of different muscle fibre types, and in muscle of clawed frogs (*Xenopus laevis*), he described contractile properties of five different fibre types and related these to their myosin composition. Thereafter, his major research interest was muscle fatigue and recovery; his research team, which includes the authors of this obituary, revealed several cellular mechanisms, ranging from decreased activation to impaired function, of the contractile machinery.

Jan was an engaged and popular teacher who spent hours producing the perfect slides for a lecture, only to replace them the following year. He was the major driving force behind a popular Swedish physiology textbook, which is still used by numerous students each year. Outside of work, Jan enjoyed running and, in the winter, skating on the natural ice of the archipelago outside Stockholm. Later in life he and his second wife, Britta Wingård, were part of a competitive veteran quiz team and enjoyed playing golf and travelling. He is survived by his wife Britta, three children, and three grandchildren.

Written by Håkan Westerblad and Joseph Bruton, Karolinska Institutet, Sweden.

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