PN
Physiology News

Issue 117 / Winter 2020

# Space physiology: To Mars and beyond

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# Welcome to the Winter 2020 edition of *Physiology News*

## Introduction



## News and Views



## Events



## Features



## Membership



**Cover image:** "Knowledge Space" by Martin Sati. See more of his artwork at **martinsati.com**

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# Space is in the air

*Ronan Berg*

Guest Editor, *Physiology News*

The Second Space Age is here! As we have just celebrated the 50th anniversary of the first manned Moon landing in 1969, it should be clear to anyone that there is a buzz around anything related to space travel these days. Almost every day, studies on astrophysics, astrobiology, and space physiology are published in major scientific journals and often make the news headlines, and I would argue that at least three of the recently awarded 2019 Nobel Prizes are related to space science. The Nobel Prize in Physics was specifically awarded within astrophysics, including "the discovery of an exoplanet orbiting a solar-type star". To my excitement, the Nobel Prize in Physiology or Medicine was awarded for "discoveries of how cells sense and adapt to oxygen availability", which undeniably poses a major challenge in relation to human space exploration! Lastly, The Nobel Prize in Chemistry was awarded for "the development of lithium-ion batteries", and less than two weeks later, the acclaimed comparative physiologist Jessica Meir took part in the first-ever all-female spacewalk to install lithium-ion batteries at the International Space Station's exterior. As it turns out, the members of the Editorial Board have also contracted this space fever epidemic, and it is therefore with gratitude and pleasure that I introduce the Space Physiology Special Issue of *Physiology News*, which I literally believe to be "out of this world" due to the kind efforts of its many skilled contributors.

The concept of a Second Space Age is controversial, but is nonetheless often described as a "gold rush to the stars" that involves both government-funded agencies, including the US National Aeronautics and Space Administration (NASA) and the European Space Agency (ESA), as well as private companies from multiple nations that aspire to explore space beyond the Moon, establish permanent extra-terrestrial habitats, and take advantage of the unlimited resources in space. This contrasts with the largely geopolitically driven space race of the First Space Age which set off when the Soviet Union launched Sputnik 1 in 1957, and arguably peaked with the six manned Moon landings as part of NASA's Apollo programme between 1969 and 1972. Furthermore, it ultimately led to the currently more than 19 years of uninterrupted human presence in space on the ISS. Now, the Artemis lunar exploration program, which is run by NASA in collaboration with ESA and several other space agencies as well as different commercial partners, has set out to bring humans back to the Moon within the next decade. This will conceivably be the first step to establish a lunar gateway, from where a manned mission to Mars can be launched in the 2030s.

The challenges that must be overcome before humans can set foot in the Martian deserts and perhaps travel further into deep space are multifarious, notably because space is an extremely hostile environment to all known forms of life. Or as the notorious Dr. Leonard "Bones" McCoy puts it in *Star Trek*: "Space is disease and danger wrapped in darkness and silence".Indeed, life as we know it has evolved and adapted within Earth's atmosphere and gravitational field, and thanks to decades of research using both Earth-based simulations and actual experiments in space, we now have substantial knowledge about how the physiology of the human body is affected by their absence, both acutely and over extended periods of time.

Together, the feature articles of this issue of *Physiology News* contend that the main physiological stressors during long-term space travel are zero-gravity and ionising radiation, which detrimentally affect practically all organ systems of the human body. As also highlighted in the recent *NASA Twins Study*, notable changes occur on subcellular, cellular, and organ levels, and lead to severe neurocognitive deficits, impaired vision, severe orthostatic intolerance, sarcopenia, and osteoporosis, to mention a few. As also posited in a previous article in *Physiology News*, this does in a sense represent a state of severely accelerated ageing (*Physiology News* **98**, 26 – 29). Once an astronaut crew has completed the approximately nine-month-long journey to Mars, there is a considerable risk that they will not be fit to complete the mission upon arrival, unless effective physiologically-based preventive measures are developed. Indeed, this is a *sine qua non*, if mankind is to survive, thrive, and multiply in extra-terrestrial environments.

With this in mind, I would add to the buzz by quoting the Russian scientist Konstantin Tsiolkovsky; a Century ago when modern aeronautics was still in its infancy, he wrote: "Man will not always stay on Earth; the pursuit of light and space will lead him to penetrate the bounds of the atmosphere, timidly at first, but in the end to conquer the whole of solar space" (*Beyond the Planet Earth* [1920]). From the current Space Physiology Special Issue of *Physiology News*, I hope you gather that among the numerous scientific fields that are required to accomplish this, the Second Space Age places physiology at centre stage.

# Looking on back on a great year

*Bridget Lumb*

President, The Physiological Society

The beauty of the discipline of physiology is the breadth it covers, uniting researchers in diverse subject areas to solve crucial issues about the health of everyone inhabiting our planet. This diversity means it is relevant for all ages – cradle to grave, from school-children fascinated by what happens to our bodies when we travel to space, through to grandparents benefiting from government policies that harness physiological research on healthy ageing. This year at The Physiological Society, we have leveraged this diversity, while also recognising the importance of supporting the communities within the broad umbrella of physiology.

## Our events

In March we held the Life Sciences 2019 conference in collaboration with the British Pharmacological Society and the Biochemical Society, bringing scientists together around the subject of post-translational modifications (PTMs). As PTMs have implications throughout the body – such as in neuronal signalling, cardiac function, circadian rhythms, and diseases including cancer and psychiatric disorders – this was an opportunity for networking across the life sciences and learning from research areas adjacent to participant's own.

Our Annual Conference, Physiology 2019, held in July in the welcoming city of Aberdeen was a fantastic showcase for the quality and breadth of physiology being undertaken by the membership and colleagues. The buzz was palpable throughout the meeting, with plenary and keynote lectures covering diverse aspects of physiology, as well as standing room only professional development sessions. You could say that the ceilidh at the conference dinner served as an extended networking session, with researchers of all career stages swinging each other around the dance floor.

Our focused conference of the year, Extreme Environmental Physiology, was held at the beginning of September in Portsmouth and could not have come at a better time, with the world finally seeming to grasp the urgency of fighting climate change. With sessions on cold, heat, hypo- and hyperbaric physiology, micro-gravity and cross-adaptation, as well as each session including physiology, pathophysiology and comparative physiology, this conference brought together internationally renowned speakers, new researchers, comparative biologists and physicians and highlighted the importance of integrated physiology.

To close the year, our conference geared towards early career physiologists, Future Physiology, was held for the second time, this year at Liverpool John Moores University in December. This conference gave early career researchers the chance to organise a stimulating two-day scientific meeting featuring their peers, as well as more senior scientists. This year's chosen topic was "Translating Cellular Mechanisms into Lifelong Health Strategies". Speakers gave insight into their current work and shared information on their career path to inspire the early career physiologists present. By encouraging physiologists to collaborate with clinicians and policymakers, the conference also helped to further the cause of healthy ageing.

As part of our aim to share physiology more widely, we hosted NASA astronaut and physiologist Jim Pawelczyk for our President's Lecture in July. This public engagement event held at the prestigious Royal Institution also included a range of outreach activities that showcased space physiology and were delivered by our Members. Read more about Jim and his career on page 10.

## Shaping policy

As the topic of Future Physiology illustrated, the impact of physiological research reaches well outside the laboratory. The policy work of The Society leverages this broad impact of physiology, as illustrated by two of our main projects this year.

The first of our policy projects, entitled "*Sport & Exercise Science Education: Impact on the UK Economy*", was a joint commission with GuildHE, the UK's registered body for smaller and specialist universities and colleges. The report found that Sport and Exercise Science (SES) courses provide enormous contributions to the UK economy – to the tune of almost £4 billion every year, supporting almost 150,000 jobs. Research undertaken in SES departments helps tackle global health challenges, such as obesity, diabetes, cancer and depression. As The Physiological Society, we must do more to share these insights within our universities and with the public as a whole. As The Physiological Society's membership continues to grow and expand, Sport and Exercise scientists will play an important role as we seek to reflect the impact of their physiological research.

Our other key policy project focused on the topic of healthy ageing, which was identified by The Society as an area of public policy which would benefit from increased involvement from The Society and its Members' research. The aim of this project was to identify ways in which physiology can support the UK Government's Healthy Ageing Grand Challenge target of an average of "five healthier, more independent years by 2035". The final report *Growing Older, Better* covers four main themes: the variety of physiological research currently being undertaken into ageing, the funding landscape for physiology, the importance of interdisciplinary working to improve our understanding of healthy ageing and how to best integrate current physiological understanding into public health guidance. The report has been designed to be relevant to a number of different audiences, with a particular focus on funders and policymakers.

## Building our community

In 2019 we sought to shine a spotlight on the importance of the individual communities within our broad discipline. We re-launched our Themes to provide a focal point for these communities and encourage support and interactions. Our Themes are Cardiac and Vascular Physiology, Epithelia and Membrane

Transport, Human Environmental and Exercise Physiology, Endocrinology, Metabolic Physiology, Neuroscience, and Education and Teaching. Each of these Themes is associated with a number of Specialities, and there is a matrix on our website **physoc.org/themes** that clearly explains how these two groupings work together to provide flexibility. We have a fantastic group of Theme Leads, who are your point of contact, and also help us plan for the best scientific content, tailored to the Themes, at our upcoming events. Members who have signed up to Themes will have received dedicated newsletters from their Theme Leads.

## Governance structure

In July of this year, we launched our new governance structure, designed to improve how The Society operates and, importantly, to establish structures that have the potential to increase inclusivity and Member participation. We have created a clear, modern and legally compliant set of governing documents that reflect best practice. Our new Articles of Association improve our transparency and enable us to become more inclusive. We believe these Articles, and the supporting Regulations, will best serve The Society and our Members to deliver on our vision of Physiology Flourishing. Trustees presented these new Articles to Members for approval at a General Meeting in December, and were officially approved in January.

## New website launched

We were excited to launch our newly designed website in June. Not only does it deliver on visual appeal and act as our "window on the world", it also allows Members to easily find the content they are looking for. We have a brand new careers section highlighting the exciting and varied career options in physiology, as well as directory of Society Representatives with which members can search for the Representative at their relevant institution.

## Diversity

The Diversity Special Issue of *Physiology News*, published in July, focused on the immutable characteristics of sex/gender, ethnicity/race, age, disability and LGBTQI+ within the STEM community. By featuring articles on a broad mix of science and the experiences of scientists/educators/students, as well as covering issues and policy around diversity and inclusion in STEM, we hoped this issue would allow everyone to feel part of the conversation by either relating to some of the experiences of the authors or by stepping outside of comfort zones to confront our own actions and those of our colleagues and institutes. In the combined years of our Editorial Board, never has there been a topic that elicited so much audience engagement, so we have since been continuing to commission content on this topic for our Members and wider audiences on our blog.

In the year ahead we look forward to strengthening our community of Members. From Europhysiology 2020 in Berlin in September, which will bring together the global physiology community, to our policy plan to build on the Growing Older, Better report, we are on track for yet another successful year. We hope you will join us as The Society seeks to deliver our vision of "physiology flourishing".

**Check out the space physiology career resources on our website: physoc.org/spacephysiology**

# Letters to the Editor: Arthur John Buller

Stanley Salmons
Emeritus Professor of Applied Myology, University of Liverpool, UK

Your Autumn issue (*PN* 116) carried a fine obituary of Arthur J Buller.

Arthur's seminal work with Jack and Rosamond Eccles in Canberra established the plasticity of skeletal muscle. In the resulting paper[1], the role of impulse activity was carefully considered but rejected in favour of a chemical trophic influence of motor neurons innervating fast and slow muscles. This hypothesis gained widespread acceptance and was the dominant paradigm throughout the 1960s. Unsurprisingly, a subsequent attempt in Canberra to demonstrate an effect of impulse activity by applying external stimulation for 10 minutes per day was met with limited success[2]. It was the development of an implantable stimulator[3] that made it possible to stimulate intact fast muscles continuously over a period of weeks, and this revealed unequivocally the profound influence of impulse activity[4,5]. By postulating that the removal of such activity allows a muscle to return to a default fast state one could counter most of the original arguments for rejecting the role of impulse activity.

There remained one issue, stated in the original Buller, Eccles and Eccles paper: "It certainly would be surprising if the sharp differentiation of muscles into fast and slow types were affected by such a relatively variable factor as the aggregate number of impulses fired by tonic and phasic motor neurons." At a meeting in Konstanz in 1979 I introduced the idea that the relationship between activity and muscle type was non-linear, a consequence of which was a threshold for change from one type to the other[6]. Arthur Buller was in the audience. He greeted me afterwards and fully embraced this explanation, a response that illustrates well his open-mindedness and generosity.

Buller and his colleagues made valuable confirmatory observations of the original effect[7]. However, it would take a greater variety of experimental approaches (recently reviewed[8]) to achieve full recognition of the role of impulse activity and to displace the strongly entrenched support for the chemotrophic hypothesis.

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# Reports of The Society's recent committee meetings

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

## Council

**4 June 2019**

The President (Bridget Lumb) reported back on the successful trip to the Federation of Asian and Oceanic Physiological Societies (FAOPS) at which The Society exhibited. The President and Chief Executive (Dariel Burdass) had utilised the opportunity to meet with the President of The Physiological Society of Japan, The President of the Korean Physiological Society, the President of FAOPS and the President of IUPS and fostered a positive relationship and noted the enthusiasm with which The Society's presence was greeted, as the *Journal of Physiology* brand was widely recognised.

The Head of Policy & Communications (Andrew Mackenzie) reported that The Society had collaborated with Guild HE on the report "Sport & Exercise Science Education: Impact on the UK Economy".The official launch had been held at Westminster and hosted by the Shadow Minister for Higher Education, Further Education and Skills – Gordon Marsden. The event had been a great opportunity for networking. The President thanked staff and Mike Tipton for their efforts in creating a quality piece of work.

The Publisher (Sally Howells) reported on the new, engaging video feature from *The Journal of Physiology* called "Physiology Shorts" which aimed to deliver short, informative research snapshots directly from the authors of research papers. The videos have been well received, both in terms of the number of views and social media engagement.

A specialist legal governance advisor from BDB Pitmans joined the meeting and spoke about the revised Articles of Association and Regulations setting out how The Society could create a clear, modern and legally compliant set of governing documents that reflect best practice as well as enabling The Society to improve transparency, inclusion and agility. The Board approved the revised Articles and Regulations drafted by BDB Pitmans and also agreed that BDB Pitmans should submit the regulated alterations to the Charity Commission.

The Honorary Treasurer (Frank Sengpiel) provided a summary of the key financials reported in the Trustee Annual Report (TAR). The Board approved the 2018 TAR for signature and submission to Companies House and the Charity Commission.

The Chair of the Membership Category and Journey Review Task and Finish Group (Rachel Tribe) gave an interim report on progress to date. The first meeting had focused on reviewing data and looking into the early stages of the membership journey and explored how to encourage longevity and loyalty. Surveys were in development to understand the motivations of non-members who attend Society meetings and to further understand the areas for membership growth. It was noted that the final report would be submitted to Council in December.

The Board discussed the imminent website launch and acknowledged it as a multifaceted platform that would constantly evolve and consequently approved a soft launch of the site. The President thanked the staff website team, the President-Elect, David Patterson and Chairs of the Committees for all their hard work on the website.

**18 September 2019**

The Board received attendee figures, feedback and communications analytics on our Annual Conference, Physiology 2019 (P19). The Chair of Conferences Committee (Sue Deuchars) commented that not only had the quality of the science been highly regarded, but P19 had also reinstated the strong sense of community that The Society is known for and the welcome received by local Members and the city of Aberdeen had created an energy that had lifted the experience. She noted that the combination of a strong leadership presence in the Trustees, the visibility of the Theme Leads as well as the presence of staff added to the "family feel".This inclusive atmosphere was particularly important in creating a good first experience for the Undergraduate Members who The Society hopes to nurture throughout their membership journey.

Following an overview from the President on the success of the President's Lecture, the Chair of Education, Policy and Public Engagement Committee (Sarah Hall) and the Head of Professional Development and Engagement (Chrissy Stokes) reported back on the successful uptake of the schools' competition and the interactive activities. Feedback from the event demonstrated that 100% of those who completed the survey enjoyed the event, knew what physiology was compared to before they attended and would attend another event.

The Board recognised the contributions of Jim Pawelczyk as not only had he given the President's Lecture but he also attended Extreme Physiology where he gave the Public Lecture, chaired a session, interacted with presenters at the poster sessions and judged prizes. During his time in the UK he had also assisted in creating a "careers in physiology" video for the website, and an interview for *Physiology News*.

The Board received the M7 Management Accounts and reforecasts and acknowledged the 2020 – 2022 financial planning process. They reviewed the key risks presented to them as part of the biannual risk review undertaken by the Senior Management Team and approved a new Conflicts of Interest Policy in line with governance best practice.

The Board also approved the terms of reference for the Nominations Committee, History and Archives Task Force, *In vivo* Task Force and the Theme Leads.

Following the launch of the new website, the Head of Policy and Communications presented figures comparing traffic on the new website with the old one. Compared to the same period in 2018, the new website had a 46% increase in users, 50% mobile traffic increase, 127% home page visit increase and a 45% increase in visits to the "What is Physiology" page.

## Finance Committee

During a meeting on 11 September 2019, Finance Committee (FC) received and discussed the July 2019 management accounts. They also reviewed The Society's cash flow management which seeks to maximise bank interest while maintaining sufficient working capital liquidity. FC discussed the latest risk management report and was satisfied with the mitigation plans in place and the recommended course of action for submission to Council. To maintain the requisite level of active Trustees, Charlotte Haigh agreed to join FC. Dean Sewell becomes the new

Inclusion and Diversity Champion and Havi Chichger the new Membership Champion.

## Education, Public Engagement and Policy Committee

The first meeting of the new Education, Public Engagement and Policy (EPEP) Committee took place on 25 September 2019. The Chair welcomed all participants. The Committee received its Remit and Terms of Reference, along with those of the History and Archives and *In Vivo* Task Forces, which now report to EPEP. Updates were presented on a number of ongoing projects that fall under the remit of EPEP, including the healthy ageing policy work, careers research project and grants review. The Committee also discussed proposals for strategic projects in 2020 including follow-up work informed by the healthy ageing policy project, further work on the 'Reward and Recognition' of Teaching in Higher Education, and various scoping projects considering how The Society might develop its professional development opportunities for early career physiologists in future. Committee members then offered their own ideas for projects that might help The Society achieve its Strategy, which will be developed into proposals for discussion at the next meeting. This meeting finished with an update from the Scientific Editor of *Physiology News*, which included a discussion on how content can be made more discoverable and accessible for use as a free resource in the future.

## Conferences Committee

The recent meeting of the Conferences Committee was held on 17 October and was chaired by Sue Deuchars, University of Leeds, UK. The first action of the Conferences Committee was to decide the recipient of the 2019/2020 GL Brown Prize Lecture.

The committee then considered the proposals submitted for the two pre-symposia hosted by The Physiological Society at Europhysiology 2020. It was noted that we will host symposia on the Themes of Human Environmental and Exercise Physiology and Neuroscience. A proposal was selected for each Theme.

The current programme for Europhysiology 2020 was noted, and outstanding plenary and keynote speakers were discussed. An update was given on Europhysiology 2022, to be held in Copenhagen. Other conferences for 2020 were confirmed as Processing and Modulation of Sensory Signals: From the Periphery to the Cortex to take place in London in June 2020, and a conference on the topic of Regeneration to take place in Edinburgh in December. The current programmes for these conferences were discussed and revisions decided on. A Future Physiology conference will also be held in July 2020. The Committee agreed that Brighton would be a good location for this meeting.

Suggested actions to improve the environmental sustainability of The Society's meetings were discussed. The Committee received the suggestions positively.

Introduction of an Equality, Diversity and Inclusion (EDI) code of conduct, a regular slot for an EDI-focused workshop and pronoun stickers were three recommendations put to the Committee to improve the equality, diversity and inclusion of our conferences. The Committee agreed to the recommendations but questioned if our current code of conduct could be modified to consider EDI rather than creating a new document.

The structure for the 2021 conferences was discussed. The Committee decided that there will be pre-symposia attached to Physiology 2021, a Future Physiology conference, a conference about the biological basis of elite performance, and a conference on a "hot topic", for which there will be an open call to members.

The Committee reflected on the impact of researchers withholding information when presenting unpublished data. The decision was made that it would negatively impact the value of our conferences and that presenters should be completely transparent so that robust and novel science is always shared.

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### A rationale for a plyometric exercise countermeasure in planetary exploration missions

The mechanical unloading experienced by astronauts in the presence of low gravitational fields (hypogravity) causes muscle atrophy and bone loss. This so-called musculoskeletal deconditioning is offset, but not prevented, by aerobic exercise (e.g. running on a treadmill). Therefore, additional exercise programmes are likely needed to preserve musculoskeletal homeostasis in space. Using a Verticalised Treadmill Facility to mimic various levels of hypogravity, researches have demonstrated in eight participants that hopping produces muscle contractions forceful enough to avert musculoskeletal deconditioning. Interestingly, they show that the greater the hopping height, the more beneficial the exercise. Further work is needed to ascertain whether analogous hop heights and beneficial effects are attainable in hypogravity.

DOI: 10.1371/journal.pone.0211263

### Impact of prolonged spaceflight on orthostatic tolerance during ambulation and blood pressure profiles in astronauts

Orthostatic intolerance (OI) is characterised by low blood pressure (BP) and light headedness when upright, symptoms that are relieved when reclining. While astronauts initially demonstrate OI upon their return to Earth, the chronic effects of prolonged spaceflight on OI are largely unknown. In this study of 12 astronauts, researchers monitored BP prior to, during, and following 6 months in space. Systolic BP decreases in spaceflight and returns to normal upon landing, while diastolic BP is unaffected. After spaceflight and during regular activities of daily living, OI does not occur, and the researchers attribute this to effective exercise programmes during and following spaceflight.

DOI: 10.1161/circulationaha.119.041050

### NASA's Mars 2020 will hunt for microscopic fossils

Mars 2020 is NASA's next Mars rover due for launch in the summer of 2020. After arriving in 2021, it will explore the red planet in an attempt to determine whether life ever existed on Mars. It's landing site will be the 45-km-wide Jezero Crater.

*Physiology Feed continues on page 13.*

# Physiologist among the stars: A conversation with Jim Pawelczyk

*Ronan Berg*
Guest Editor, *Physiology News*

*Julia Turan*
Managing Editor, *Physiology News*

Jim Pawelczyk is one of the very few with the credentials of a physiologist who has also served as an astronaut. In 1996, he took a leave of absence from a position as Assistant Professor of Physiology and Kinesiology at Penn State University, as he was given the chance to enter the NASA astronaut programme. Having grown up in the 1960s in the United States, he had been glued to the television to watch any launch; like many other children of that generation, it was not an opportunity he was going to pass up.

Two years later he spent 16 days in orbit as part of the seven-person crew of Neurolab, the final mission of the European Space Agency developed SpaceLab module flown by the space shuttle Columbia. The flight orbited Earth 256 times, and the crew conducted 26 experiments mainly on the effects of microgravity on the brain and nervous system, serving both as research subjects and operators. Two decades on, Pawelczyk remains an optimist who firmly believes that we will be able to overcome the physiological challenges associated with a manned mission to Mars, so that we can set foot there in the 2030's. *Physiology News* met Pawelczyk in London when he was in the UK to give The Physiological Society's President's Lecture "What Price a Martian – Human Limits to Exploring the Red Planet".

Looking back at the Neurolab mission, which was incepted in what President George HW Bush declared the "Decade of the Brain", Pawelczyk is still thrilled by the results of the experiments that focused on one of his own principal areas of research, the neural regulation of the cardiovascular system. These experiments sought to elucidate the mechanisms of orthostatic intolerance experienced by astronauts after spaceflight, which at the time was widely believed to be caused by a reduction in sympathetic output to the cardiovascular system triggered by prolonged microgravity:

"Our hypothesis was that we were going to have this reversible form of autonomic dysfunction if you will. That is tremendously exciting, at least in theory, because autonomic dysfunction is not reversible. Once you've got it, you've got it, and all you can do is manage it. So if indeed it was reversible, think what that might mean for those half a million Americans that have problems associated with poor blood pressure regulation."

In the experiments, the Neurolab crew obtained direct recordings of sympathetic vasoconstrictor nerves and noradrenaline kinetics on each other. But to their surprise, there were no signs of autonomic dysfunction: compared to pre-flight measurements obtained in supine position on Earth, there was actually a slight increase in sympathetic activity. Or as Pawelczyk laconically puts it:

"A beautiful hypothesis ruined by data!"

For Pawelczyk, the results of the Neurolab experiments focusing on the neural regulation of the cardiovascular system fundamentally changed the perception on the adaptive responses of the autonomic nervous system to prolonged microgravity, and were subsequently published in three back-to-back papers in the January issue of *The Journal of Physiology* in 2002.

To this day, Pawelczyk remains a dedicated advocate for the continued research on the impact of the space environment of the human body, and has testified before the US Senate on several occasions, arguing in favour of funding and conducting such studies on astronauts at the International Space Station. Pawelczyk explains why he considers research in space so important:

"In my opinion, the main reason is so that we can keep crews healthy to explore further and faster. Having said that, things that we do and learn in space, do ultimately have an effect."

With reference to the interviewee's glasses, Pawelczyk elaborates:

"That scratch resistant coating that you have on your lenses was originally created to coat visors of astronauts in flight... NASA engineers


Neurolab was the module of the Spacelab mission focusing on the effects of microgravity on the nervous system, which Pawelczyk was part of.


Astronaut and physiologist Jim Pawelczyk gave our 2019 President's Lecture. Over 200 members of the public enjoyed his fascinating talk and this was followed by hands-on activities related to physiology and space.

said, we've got to make sure that we protect these visors because our people need to see well [...] when they are outside the vehicle. Somebody else got the bright idea and said, well you know we could take eyeglass lenses on the ground and use the same material to make them scratch resistant."

Indeed, the problems experienced by astronauts in space are manifold. And while Pawelczyk has studied the effects of prolonged microgravity on the human body as a physiologist, it is thus also a personal experience in his case. Perhaps somewhat surprisingly, a main problem experienced by the astronauts, including the Neurolab crew, was back pain. Many consider this to be related to the marked elongation of the unweighted spinal column – indeed astronauts usually "grow" several inches taller during missions. Pawelczyk's experience was, however, quite different. One night, while sleeping in his sleeping bag which he had tied to a rail in SpaceLab, he woke up "with the worst back ache of his life":

"It was terrible. [...] You are sleeping with gravitational forces not really acting on you, so that the body posture that you assume is not defined by gravity, but by muscle tone."

It turned out that the gluteal muscle group was the culprit:

"The most wonderful thing about physiology is that we are confronted with it every day, every moment"

"The gluteus has muscle tone, so you sort of create this big lordotic curve when you're in space, so you're arching your back. And guess what? You wake up in the middle of the night with a big back ache. So the answer to that is you bring your knees up and you put a strap around your body, keep your knees up in position. Maintain more of a natural, normal curvature of your spine – and then everything is fine."

As our conversation comes to an end, Pawelczyk reflects on what advice he'd give to young physiologists out there – who may or may not become astronauts:

"[...] I think particularly for budding physiologists, *always be curious*. The most wonderful thing about physiology is that we are confronted with it every day, every moment, because we're physiological beings. We are a discipline that asks 'why' and 'how' all the time, relentlessly, and we should never stop asking or trying to answer those two questions."

*Jim Pawelczyk was born in Elma, New York, USA, in 1960. He graduated with a BA in biology and psychology from the University of Rochester (1982), followed by a MSc in physiology from Pennsylvania State University, and PhD in biology/physiology at the University of North Texas (1989). Following a postdoctoral fellowship in cardiovascular neurophysiology at the University of Texas Southwestern Medical Center (1989 – 1992), he became Assistant Professor of Medicine at the University of Texas Southwestern Medical Center and Director of the Autonomic and Exercise Physiology Laboratories at the Institute for Exercise and Environmental Medicine and Presbyterian Hospital of Dallas (1992 – 1995). Since 1995, he has served as Assistant, and now Associate, Professor of Physiology and Kinesiology at the Penn State University. In 1996, he started astronaut training at NASA, and from 17 April to 3 May, 1998, he spent 15 days 21 hours and 50 minutes in space as part of the payload crew on the space shuttle Columbia.*

# Physiological discoveries abound within NASA samples

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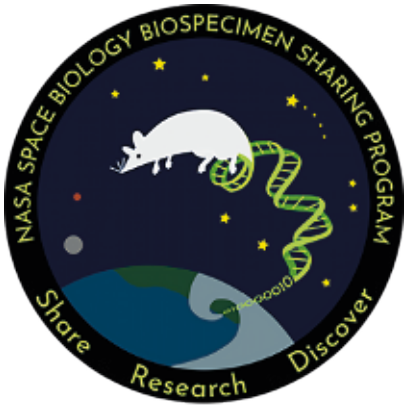


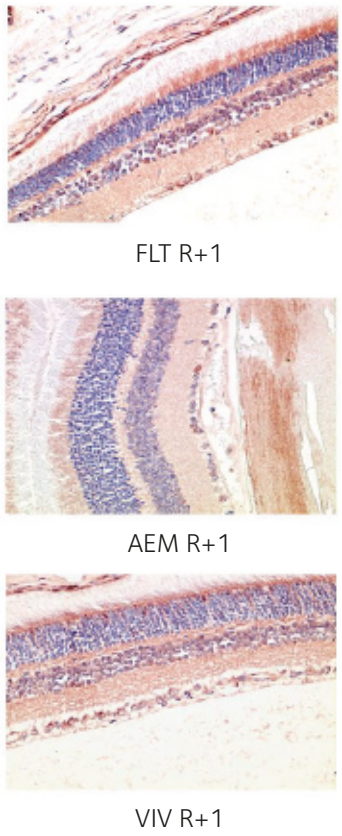


*Figure 1.* Previous examples from ISC-BSP Tissue and Data Sharing. Left: Images of histological mouse retina sections stained (red-brown) for caspase-3 from STS-133 treatment groups Flight (FLT; R+1), Animal Enclosure Module (AEM; R+1), and Vivarium-housed (VIV; R+7). © Zanello *et al.* (2013). Right: A stacked bar plot showing relative abundance of microbial families uncovered in each sample (Basal, Vivarium, Ground, Flight), sorted by groups (taxa). © Jiang *et al.* (2019) and is licenced under CC BY 4.0.

Before humans risked their lives launching into space aboard the Vostok Program and Mercury Project, various organisms were flown to determine if it was possible for life to survive spaceflight. For decades, NASA, along with international partners, have continued sending biological experiments to space. Potential biological hazards from spaceflight include decreased gravity, increased exposure to radiation, altered light-dark cycles, and loads experienced during launch and landing. It is imperative to understand the basic science and health risks associated with spaceflight, along with developing countermeasures, as humanity ventures back to the Moon, and then to Mars and beyond.

NASA Ames Research Center houses an Institutional Scientific Collection (ISC) of spaceflight biological specimens and tissues. Through NASA's Biospecimen Sharing Program (BSP), the samples in this biological repository are available for request by all researchers, including those based outside the United States.

A number of newly identified biological knowledge gaps and astronaut health risks have emerged from extended exposure to microgravity from long-duration missions. Of particular concern to NASA is the loss of visual acuity, which a significant number of astronauts have unexpectedly experienced. NASA is keen on getting researchers to work on elucidating the underlying cause(s) of this issue. In an effort to further the research progress on this topic, the NASA BSP coordinated the sharing of mouse eyes from the STS-133 Shuttle mission. The study led by Susana Zanello[1] conducted histological examinations of the mouse eyes from post-flight days 1, 5 and 7. Gene expression analysis suggested that reversible molecular damage occurs in the retina of mice exposed to the spaceflight environment, and that protective cellular pathways are induced in the retina and optic nerve in response to these changes. While correlation of research findings in the mouse tissues to human astronauts presents a set of challenges,

> "Through NASA's Biospecimen Sharing Program, the samples in this biological repository are available for request by all researchers, including those based outside the United States"

"Observations from her analyses shed light on the specific environmental factors that contributed to a robust effect on the gut microbiome during spaceflight, with important implications for mammalian metabolism"

the mouse model is an excellent way to characterise underlying changes at the cellular and molecular levels that are simply not available with the human crew.

The costly effort of sending organisms into space makes space-flown biological specimens a rare and valuable resource. Quite often, when life science samples are retrieved from completed missions, there are surplus tissues which remain unused by the Principal Investigators and collaborators. In this scenario the tissues are harvested, preserved, and archived in the NASA ISC at the Ames Research Center to ensure the maximum scientific return from space missions in the belief that new discoveries can be made from the samples.

An important recent finding was made possible by the study of what would have previously been considered waste: rodent fecal pellets. Through NASA's BSP, Martha Vitaterna, from Northwestern University obtained mouse fecal pellets from a 37-day mission aboard the International Space Station and examined them for the effects of spaceflight on gastrointestinal microbiota[2]. Findings from previous studies have demonstrated a change in the gut microbial diversity and community structure during spaceflight, but it was unclear what the functional relevance of those microbiome changes were. Using 16S rRNA gene amplicon sequencing, Vitaterna and her team profiled the microbiome of the fecal samples. They then compared the microbiome changes to other relevant datasets and integrated the gut microbiome data with publicly available transcriptomic data in the liver of the same animals for a systems-level analysis. Observations from her analyses shed light on the specific environmental factors that contributed to a robust effect on the gut microbiome during spaceflight, with important implications for mammalian metabolism.

**Available tissues for physiology research**
The NASA ISC at Ames Research Center currently stores over 32,000 specimens. Most come from Shuttle and International Space Station flight investigations, but also included in the collection are ground-based specimens from spaceflight-model experiments. Tissues are predominantly from mice and rats, though samples are also available from bacteria and quail. The specimens include tissues from many systems including musculoskeletal, neurosensory, reproductive, respiratory, circulatory, and digestive. The samples are stored at -80°C, -20°C, or +4°C, depending on the fixative used. Detailed metadata are available for all samples. Historically, these tissues have been used for a wide range of analyses, including histology, genomics, and transcriptomics. The NASA Ames Life Sciences Data Archive (ALSDA) has been shipping samples to investigators since 1995.

**How to request tissues from the NASA ISC**
Tissue requests are initiated by submitting an online Biospecimen or Data Request. If the requested tissues are available, the requestor will be sent instructions for submission of a short proposal. Visit the NASA ISC website for more information: **nasa.gov/ames/research/space-biosciences/isc-bsp** Contact the ALSDA team: **arc-dl-alsda@mail.nasa.gov**

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Recently shown to contain carbonate deposits within its inner margin, Jezero may have encompassed a lake that was perhaps hospitable to life. Carbonates are calcium-rich rocks that, when stuck together with bacteria, form stromatolites. If stromatolites are detected by Mars 2020, they may provide insight into how the Martian environment has changed over time, and could offer fossil evidence of life on the red planet.

go.nasa.gov/2EEnG80

## Is oral health affected in long-period space missions only by microgravity?

Various aspects of spaceflight, including microgravity, radiation, stress, and isolation, may adversely affect the oral physiology of astronauts. In this systematic review, 12 studies were surveyed for evidence of the effects of microgravity during short- and long-term spaceflight on oral health. During short spaceflights, the stress hormone cortisol is elevated, as is the antibody IgA in saliva. Long-term missions are associated with changes in the oral microbiome, with greater anaerobic bacteria (e.g., *Streptococcus mutans*) present in astronauts' dental plaque and saliva. The authors warn that such changes may promote oral pathologies that could compromise long-term space missions, and recommend that appropriate preventative measures are utilised to mitigate this.

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## Space farming

For sustainable human space colonisation we must develop the means to produce food that meets all our nutritional requirements. To date, several vegetables such as peas, wheat, bok choy (Chinese cabbage), mustard and several lettuces have been successfully grown in space. This list continues to grow with NASA announcing it will soon test its first fruiting plant, namely the Española chilli pepper, in an effort to alleviate food boredom and provide a vitamin C boost to their astronauts. SpaceX will send hemp and coffee plant tissue cultures to the ISS in March 2020 to explore how their metabolic pathways and growth are affected by microgravity. Researchers have also shown that it is possible to grow crops such as tomato, quinoa and radish in simulated lunar and martian soils, but perhaps the strangest of all farming endeavours was the successful proof-of-concept Russian–Israeli collaboration to grow and 3D print beef "meat".

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# Sex in space: Our final reproductive frontier

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Over recent decades, our ability to regulate and manipulate our own reproduction has expanded significantly. We have developed the ability to collect and manipulate gametes, fertilise the oocyte outside of the body, culture the embryo in a dish and transfer it back to the uterus to continue its development. To date, over eight million babies have been born from assisted reproductive technologies (ART) such as *in vitro* fertilisation (IVF)[1]. Using ART, we are able to delay having children until a time that suits us best, putting our fertility on ice, literally.

While ART such as IVF have enabled millions of people to have a family of their own, our ability to collect and store sperm, oocytes and embryos may have one unexpected benefit, potentially helping the human race to colonise other planets. This is because sex in space is surprisingly difficult. Firstly, just staying in close contact with each other under zero gravity is hard. Secondly, as astronauts experience lower blood pressure while in space, maintaining erections and arousal are more problematic than here on Earth. If that's not enough, then the sheer lack of privacy on shuttles and space craft mean there are no rooms into which two astronauts can retreat for some time together. Therefore, it's probably not surprising that to date there have been no confirmed accounts of astronauts having had sex in space.

However, astronauts have been experimenting with reproduction for many years[2]. A range of animals have been blasted into space to see how microgravity might affect their reproduction. Initially, rats and mice were sent to see if they would mate and if their pregnancies would develop normally. Unsurprising to anyone who uses rodents to study reproduction, the significant disruption of travelling into space and back meant none of the females actually developed to term with their pregnancies. Similarly, astronauts explored whether IVF could be done using isolated mouse sperm and oocytes, or whether mouse embryos which had been generated on Earth would develop in space. However, in both cases, the experiments did not yield positive results. Separate studies conducted on the Russian space station Mir also showed that microgravity seemed to have negative effects on the eggs and embryos of a range of species including salamanders, sea urchins and quails.

Together, these studies seem to suggest reproduction in space might not be as straightforward as it is here on Earth. However, more recent experiments have approached the question of sex in space from a different position. The current thinking is to send freeze-dried sperm, oocytes or embryos across space, like an interplanetary reproductive delivery service. The simple reason for this is that frozen gametes and embryos take up far less space and resources on a spaceship than living humans do, and can potentially be stored for decades. Once at their destination, they can be revived and implanted. The downside to this is that in space, the levels of cosmic radiation are significantly higher than here on Earth. Thankfully for us, our atmosphere shields out significant amounts of solar radiation, but in space, astronauts, and their gametes, are exposed to doses hundreds of times higher than on Earth. This high-energy radiation can damage DNA, causing mutations and impairing the development of an embryo[3]. Therefore, researchers and space agencies want to know whether sending gametes and embryos on long journeys into space is safe. In 2017, researchers sent packages of freeze-dried mouse sperm to the International Space Station (ISS) for nearly 10 months[4]. When it returned to earth, they compared it to control fresh samples taken from the same mice. The first observation was that the sperm which had been on the ISS had more fragmented DNA than the control sperm. As high levels of sperm DNA fragmentation are associated with male infertility and increased miscarriage risk, these observations were a worry[5]. However, when used in IVF, the space sperm were able to generate the same number of embryos as the sperm which stayed on Earth. Furthermore, following transfer, embryos derived from the space sperm were just as able to develop into healthy adult mice as the control sperm.

The next step for some is to test the effects of microgravity and space travel on human gametes and embryos. While some may view such experiments as unethical, many believe that in order to understand the impact of space travel of human reproduction, the use of human sperm, oocytes and embryos is a necessity. In a study presented to the European Society for Human Reproduction and Embryology (ESHRE) in 2019, researchers explored the effects of microgravity on human sperm[6]. Using a specially modified plane, normally used for training astronauts, the researchers exposed 10 human sperm samples to reduced gravity. Using the same array of tests normally undertaken within a fertility clinic, the research saw there was no detrimental effect of the microgravity on sperm quality.

While such studies show that aspects of human reproduction are possible in space, there is still a long way to go before we see the whole reproductive process undertaken outside the confines of our home planet.

"The research saw there was no detrimental effect of the microgravity on sperm quality"

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# How to live in space

## by Colin Stuart

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Colin Stuart
Smithsonian Books (2018)
ISBN: 9781588346384

"A six-month stay in orbit reduces bone density by the equivalent of 10 years on earth, reduces physical work capacity by 40% and exposes astronauts to heightened cosmic radiation, increasing cancer risk"

Colin Stuart is an astrophysicist, successful author and scientific communicator. He is passionate about communicating the science of space with the public, and he is passionate about the need for interdisciplinary collaboration to advance space research. This book is a self-described space manual, describing what astronauts experience during training, the impact on an astronaut's body of living in space and the implications to any future space exploration and tourism.

There are interesting factoids throughout, many of them general knowledge, but some specifically physiological. For example, did you know – space starts 100 km above the Earth, at the Kårmån line, the point at which aeronautics becomes astronautics. It takes 9 minutes from lift-off to reach an orbit 220 km above the earth. Earth's escape velocity is 11.2 km per second, and a typical lift-off subjects an astronaut to 3G – substantial enough forces, but this pales to insignificance when faced with the typical 8G force of re-entry. In preparation for space, astronauts train underwater where the weightlessness of outer space is simulated. Training in centrifuges allows astronauts to prepare for high G-force environments. Much of this training focuses on muscle flexing and breathing techniques. Exhaling is no problem in such an environment, but inhaling is extremely difficult, so astronauts need to learn to restrict breathing to short, sharp inhales and exhales.

Another key physiological concern is the nausea associated with weightlessness. Astronauts train in the "vomit comet", where they are subjected to parabolic arc flight sequences of sharp ascents and precipitous descents while flying high above the Nevada desert. Space sickness, also known as space adaptation syndrome, affects 75% of astronauts. The degree of space sickness is very individual and is measured using the Garn scale – a scale based on the worst case ever recorded – a poor unfortunate who needed to be Velcro-ed to a wall on the International Space Station (ISS) for the duration of the trip to minimise his sickness. The cause of space sickness is the effect of weightlessness on the fluid in the vestibular organs, activating the hair cells in a manner that conflicts with visual signals, disorientating the brain and usually lasting for 2 – 4 days.

There is interesting information on how tricky it is for humans to live in space. There are details describing how oxygen is generated and carbon dioxide removed from the air and details of water recycling on the ISS. It is possible to recycle shower run off, sweat and urine from everyone on board, be they human or animal. The Russians draw the line at recycling urine, but the Americans happily drink it!

The effects of months in space on the human body is particularly fascinating. Astronauts are likely to develop chicken legs, puffy face and kidney stones. A six-month stay in orbit reduces bone density by the equivalent of 10 years on earth, reduces physical work capacity by 40% and exposes astronauts to heightened cosmic radiation, increasing cancer risk. Astronauts have to readjust to Earth's gravity in many ways upon their return – even the muscles for articulation are affected by space. The astronauts exercise for 2.5 hours daily on the ISS, with a mix of weights and aerobic exercises to minimise musculoskeletal loss, but much more research is needed to understand how to minimise the impact on long space missions.

The physical changes observed in astronauts on the ISS suggest that should humans leave Earth in search of a new home far, far away, the human body would change to adapt to low gravity – we would likely become taller, thinner, may struggle to give birth naturally and would be crippled by the high gravity conditions when returning home for a visit.

This book is a very interesting read for anyone interested in science – touching on physiology, chemistry and of course astrophysics, as well as interesting general knowledge that will be invaluable for future space tourists and pub quiz enthusiasts!

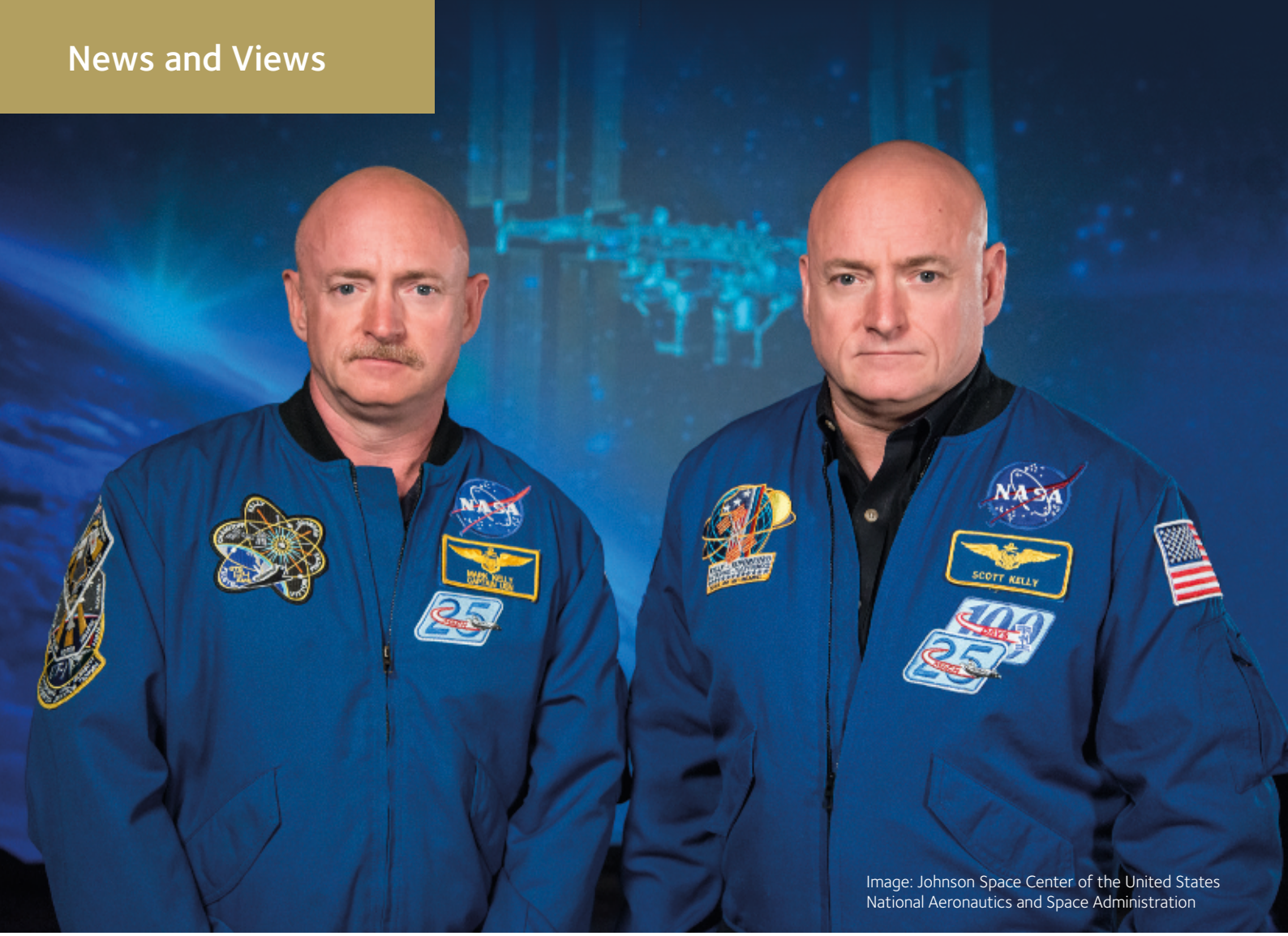


Image: Johnson Space Center of the United States National Aeronautics and Space Administration

## The NASA Twins studies

The "NASA Twins" Mark (left) and Scott (right) Kelly (b. 1964). Mark served as an astronaut at NASA from 1996 to 2011 and logged a total of 54 days in orbit. Scott served as an astronaut at NASA from 1996 to 2016, and over the course of four missions, he spent a total of 520 days in orbit. The NASA studies were a unique opportunity to study the effects of long-term spaceflight on the human body, by comparing Scott who was on board the ISS for a year, to Mark who remained on Earth during that time.

# The microbiome in space, from the Apollo missions to present

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Fifty years ago, when the Apollo 11 astronauts Neil Armstrong, Buzz Aldrin, and Michael Collins returned to Earth, they were quarantined for 21 days, including some days in a converted Airstream trailer where they celebrated Neil Armstrong's 39th birthday. This was a precautionary measure against the possibility of contagious potential pathogens ("moon germs"), a risk considered as unlikely but uncertain at the time. Following Apollo 14, this quarantine is not required, nor is testing astronauts' blood by injecting it into mice. Over the past 50 years, research approaches towards astronaut health, the physiological effects of space, and microorganisms have dramatically shifted, reflective of the explosive advancements in biomedical research during this time. These are clearly illustrated by the NASA Twins Study, and studies of the gut microbiome in space, in which we have had the privilege to be involved.

Nearly 50 years after the Apollo 11 mission, the scientific investigation of another landmark human space expedition, astronaut Scott Kelly's 342 days on board the International Space Station (ISS), culminated in a publication earlier this year in the journal *Science*[1]. This year-long mission marked the longest human spaceflight of a US astronaut, and was even more unique because Scott Kelly's identical twin brother, retired astronaut Mark Kelly, agreed to participate in the study. This provided an unprecedented opportunity to study the effects of long-term spaceflight on the human body. NASA assembled a consortium of 10 investigator teams to study the twins

in preparation for future long-term missions such as those around the Moon, asteroids and ultimately Mars.

The Twins Study exemplifies how scientific approaches have evolved over the years. Rather than ten discrete investigations, the study was designed to develop a cross-disciplinary picture of how various systems, from cognition to physiological and molecular processes, may respond, in concert with one another, to the challenge of spaceflight. The result is a rich and intriguing data set. The study was further strengthened by the ability to obtain comparable data from the "ground twin" so that an assessment of expected variability over time in a genetically matched individual with a busy, varied life on Earth could be made. In this manner, variance outside that range seen in the "space twin" could be more confidently attributed to space flight.

Spaceflight-induced microbiome changes seen in the Twins Study were modest, and quickly diminished after the astronaut returned to Earth. Nonetheless, these changes were beyond the day-to-day fluctuations in the gut microbiome composition in the ground twin during the same period of time. Many of our colleagues' other measures exhibited parallel spaceflight response profiles; future studies can test hypothesised links among these mirrored responses. Neither the integrated, multi-system approach nor the computational and molecular analyses were methods available 50 years ago.

"The Twins Study exemplifies how scientific approaches have evolved over the years"

Inclusion of the gut microbiome as a topic for this kind of integrated evaluation of the adaptation to spaceflight also would not have been imagined 50 years ago, when bacteria were primarily viewed with suspicion of pathogenicity. Now, modern high-throughput sequencing approaches reveal a dynamic, diverse and complex "ecosystem" of microorganisms inhabiting the gastrointestinal tract and interacting with mammalian physiology, that change in response to spaceflight and might in fact have the potential to help astronauts to adapt to spaceflight.

From a high-level view, some alterations in the gut microbiome in response to spaceflight are consistent across studies: an increase in the microbial diversity and a shifted microbial community structure have been identified in the NASA Twins Study[1] as well as another, subsequent astronaut study[2], and even in mice that have flown on the ISS[3]. Development of a new analytic strategy, a tool called STARMAPs, revealed that the consistencies of the effects of spaceflight on the gut microbiome go far deeper: the overall patterns of the microbial composition changes are reproducible when comparing mice flown on the space shuttle to those flown on the ISS[3]. Now, studies to integrate these spaceflight-specific effects with other, related systems can lead to an understanding of the role of the microbiome in adaptation to spaceflight. Such "small steps" of scientific progress, continuing into the next few decades, can advance health in space as well as on Earth, so that we are ready for future giant leaps for mankind.

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# Telomeres and genomic instability during long-duration spaceflight


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The first astronauts for the American (1960) and Russian (1959) space programs demonstrated that spaceflight was physiologically possible for the human body, while also inaugurating a new era of human exploration of space. This led to current-day plans for missions to the Moon and Mars, which include new commercial and government agencies (e.g. China, India, Israel), and will involve months to years of exposure to spaceflight conditions. Yet, even as we commemorate 50 years since the first landing on the Moon, very little biomedical data exist on the health effects of long-duration spaceflight, since very few missions ($n$=8) have lasted for greater than 300 days. Indeed, only four individuals have ever participated in spaceflight missions lasting longer than one year. Thus, while the effects of short-duration spaceflight on the human body have been well documented, there is a paucity of data on the effects of long-duration spaceflight, and almost no data using modern methods in molecular biology. These fundamental limitations in our knowledge, concomitant with the emergence of several new, active spaceflight agencies, helped to inspire the NASA Twins Study: a multi-dimensional characterisation of the effects of a year-long spaceflight on the body[1].

The NASA Twins Study is clearly limited in the sample size ($n$=1 per group), and thus the experiments were designed to create benchmarks that can be used in later missions to optimise crew health, improve in-flight collections, and to compare measures of acute or long-term flight risks. Data were generated across a myriad of modalities of human and microbial biology, including stool, saliva, skin, urine, and blood samples. The Study used a wide battery of measures, which included various whole-genome, RNA, and metagenome sequencing techniques, as well as proteomics and metabolomics, and numerous other techniques.

Blood analyses elucidated several physiological changes that long-term spaceflight has on the genome, including the impact on telomeres. Telomeres are repetitive nucleotide sequences found at the physical ends of eukaryotic chromosomes, which are critical for maintaining genome stability. During each cycle of cell division, telomeres

shorten due to the end-replication problem, which results in the inability to replicate to the very end of newly synthesised lagging strands. As such, telomeres serve as "buffer zones", preserving the genes that lie medial to them. However, because telomeres shorten with ageing, as well as with a variety of lifestyle factors and stresses, they eventually become so short that cells enter a state of senescence and stop dividing. This process is also associated with ageing-related pathologies such as cardiovascular disease and cancer. Interestingly, and contrary to expectation, the NASA Twins Study found that long-duration spaceflight resulted in a significant increase (~15%) in telomere length in the "space twin" as compared with his pre-flight and post-flight telomere lengths, as well as those of the "ground twin". Given that the space twin's telomeres dramatically shortened within 48 hours of returning to Earth, it is postulated that spaceflight-specific telomere elongation may have occurred in response to galactic cosmic radiation exposure; results are consistent with one other ISS study in *C. elegans*[2]. It is also worth noting, however, that while the space twin's average telomere length stabilised to approximately his pre-flight levels, cell-by-cell FISH analysis revealed an increased number of short telomeres post-flight, potentially suggestive of ongoing damage, instability, accelerated ageing and/or future adverse health effects.

Indeed, and as expected with any significant physiological stress, thousands of genes changed their expression levels during spaceflight, including pathways related to telomere maintenance, immune (T-cell) activation, and DNA repair. Moreover, of the genes that changed expression in spaceflight, ~91% returned to normal ranges within 6 months post-flight. While the overwhelming majority of transcriptional changes returned to pre-flight levels, a distinct subset of 811 genes involved in either immunity or DNA damage remained altered post-flight, which has provided insight into candidate genes that are more susceptible to extended spaceflight and which may be driving the continued re-adaptation to gravity.

DNA repair pathways and re-acclimation mechanisms are likely confounded as part of the normal response of returning to gravity, but evidence of DNA damage was observed. In the analysis of genomic instability, the space twin demonstrated increased frequencies of chromosome aberrations, particularly inversions (i.e. rearrangements within chromosomes), during spaceflight: a finding consistent with exposure to ionising radiation, particularly high linear energy transfer (LET) cosmic radiation[3,4]. Moreover, the space twin's chromosomal inversion frequencies remained elevated post-flight, suggesting continued instability and possibly radiation-induced DNA damage to multipotent haematopoietic stem cells of the bone marrow, which could have a long-term impact on the genetic health of both myeloid and lymphoid fractions. Thus, even longer spaceflight missions should involve an expanded focus on the haematopoietic systems.

"It should be possible to survive the transit to Mars and then return back to Earth"

DNA methylation has also become a widely used proxy for assessing the ageing process, with methylation "clocks" being used successfully to predict age and mortality in several different species. The addition of a methyl group to a DNA strand typically results in local cessation of transcription. Thus, methylation in a gene's promoter region is related to reduced expression of that gene, and is a common epigenetic marker of gene expression regulation. While genome-wide methylation changes in the space twin were within the range of variation of those of the ground twin, gene ontology enrichment analysis revealed enrichment of epigenetic discordance in several genes indicative of immune stress. Thus, as with previous studies demonstrating changes in the immune system of astronauts, this is an area for continued surveillance and focus on future long-duration missions.

While a full discussion of the results presented in the Twins Study is beyond the scope of this article, it is worth noting that the Study evaluated the effects of long-duration spaceflight on several other physiological areas as well. For example, in its assessment of the immunome, the Twins Study revealed that inoculation with an annual flu vaccine in space, as well as subsequent inoculation on Earth the following year, were both successful in initiating an appropriate T cell-mediated response in the space twin, thereby suggesting that the immune system's defenses are not functionally impaired by microgravity. A cognitive assessment revealed no dramatic changes in the space twin's higher cortical functions during his time in space with respect to the ground twin; upon landing, however, the space twin exhibited a pronounced decrease in speed and accuracy while performing cognitive tasks which persisted for six months upon re-acclimation. Additional analyses demonstrated that the space twin's spaceflight resulted in a 7% decrease in body mass, a dynamic osteocyte turnover rate which first increased and then stabilised during the latter six months of flight, increased inflight folate and urinary lactic acid levels, increased inflight mitochondrial DNA and ATP-dependent respiration, and increased carotid artery intima-media thickening that persisted into the post-flight period, among other findings. Additionally, the NASA Twins Study determined that cephalad fluid shifts observed in the space twin corresponded to retinal oedema, as well as elevations in urinary aquaporin-2 (AQP2): a protein involved in regulation of water resorption that might be implicated in the pathogenesis of ophthalmologic disorders observed during and after spaceflight.

In summary, the Twins Study demonstrated that the human body is extraordinarily adaptive to the changes incurred during a one-year mission, and that it should be possible to survive the transit to Mars and then return back to Earth. However, the long-term health effects of long-duration spaceflight are exceedingly difficult to assess, and more work must be done to examine whether physiological effects, such as post-flight telomere shortening, stem cell alterations, and/or genomic instability have detectable long-term adverse health effects on individuals exposed to the space environment for prolonged periods of time.

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Meeting Notes

# Partnerships, communities and inclusion to drive better research

9 September 2019,
Francis Crick Institute,
London, UK

*Lilian Hunt*

Programme Manager at EDIS (Equality, Diversity and Inclusion in Science and Health)

The EDIS Symposium 2019 was held on 9 September at the Francis Crick Institute on the theme of inclusive research and experimental design. We wanted to explore the concepts of equality, diversity and inclusion (EDI) in relation to how we fund, design and conduct research for the benefit of human health. Creating these links between EDI and research helps show how inclusivity in all its forms can improve research and health outcomes, and importantly how ignoring these ideas can actively harm them.

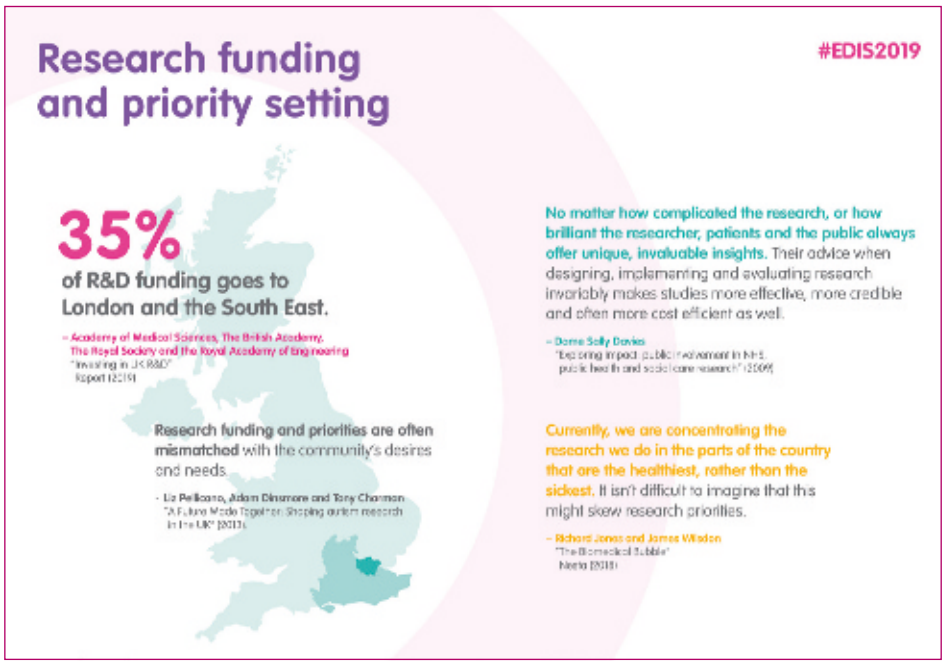
In addition, the symposium had the aim of creating an inclusive culture at the event and removing barriers to participation. We know that attending and presenting at research conferences is vital to career progression, as well as personal and professional development. We also know that some within the science and health research sector are systematically excluded from attending, contributing to or participating fully in these events. We experimented with new ideas to increase access and participation, and we've shared the different ways we did this in our delegate booklet that's available online[1].

At the EDIS symposium, Katherine Cowan, Senior Advisor to the James Lind Alliance, spoke about the need to work with researchers, clinicians, patient groups and communities together on an equal level to determine research priorities. Working in this way can fundamentally change the topics of research that are prioritised for different diseases and build understanding and mutual respect between "researchers" and "those whom research is being done to". Examples include the autism community's ask for funding to be shifted from neuroscience to social care[2], and the schizophrenia community's need for more research to be focused on tackling weight gain[3,4].

The merging of basic biomedical science with social science to better understand disease, patient and societal context is imperative. This is particularly true within the field of population genetics as it focuses more on personalised genomic medicine. However, the literature of genomics is littered with the language of social constructs such as race, and this can be a barrier to understanding. Ewan Birney presented alternative language to use within the field, moving from societal ethnic classifiers (such as "Western European") to pluralised ancestry descriptors (e.g. "European Ancestries") as a possible method to move away from current terms for ethnic groupings with genetics. Ethnic groupings are often problematic due to their poor alignment with genetics and, as they get used as proxies for genetic difference, personal and cultural contexts of diseases and phenotypes are lost.

Emma Baple also presented work in genetics on developing deep, mutually beneficial and culturally sensitive research partnerships with isolated communities. These can help to develop novel insights into known inherited diseases. These relationships take time and respect but a community, clinical, biomedical and social science interdisciplinary collaborative framework can address research and healthcare inequalities and unmet needs. Baple's team have developed a course detailing their community approach to genomic medicine and research where key concepts could be explored in other fields[5]. Findings from population-specific genetic testing can also be translated globally, reaching others whose diagnosis has so far evaded discovery through typical clinical phenotyping[6].

Understanding that, as scientists, no work is done in isolation but as part of a complex research system that is accountable to public health should be fundamental to how we work. Holding this understanding at the core of decision-making, research design and how we conduct research helps bring a people-centred approach to biomedical, medical and health research. If we include underrepresented groups, areas of unmet need and co-production in our research we are far more likely to produce results that benefit communities long-term and tackle health inequalities. The importance of inclusive research and experimental design cannot be emphasised enough; however, we must integrate biomedical, medical and social sciences to build trust and meaningful relationships to do so.

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# Europhysiology 2020
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Meeting Preview

# Europhysiology 2020: Bringing together the physiology community

11 – 13 September 2020,
Estril Congress Center,
Berlin, Germany

*Susan Deuchars*

Chair of Conferences Committe,
The Physiological Society
& University of Leeds, UK

We are delighted to be looking forward to Europhysiology 2020, which will take place in Berlin, home to world-renowned universities and a fascinating city for culture and history. Europhysiology 2020 is a continuation of a series that started with Europhysiology 2018 in London with the third conference taking place in Copenhagen in 2022. The overwhelming success of our first Europhysiology conference in London, was due in part to superb plenary and keynote lectures, thought-provoking symposia and a plethora of oral communications that highlighted the importance of interactions between the physiological societies in Europe. Our packed programme in Berlin promises to keep this momentum going and we look forward to maintaining that fantastic buzz and enthusiasm in discussing new advances in physiology research.

Based on Europhysiology 2018, we expect more than 1400 participants involved in all aspects of physiology. This is your chance to broaden your network of physiology colleagues and hear the latest research across the full breadth of research topics. There are over 100 oral communication slots and three poster sessions that allow physiologists of all career stages to showcase their research. These, together with the workshops and the informal events being planned, both across our Themes and across the societies, will encourage mingling, lively discussions and fostering of collaborative ventures similar to those that have already proved fruitful from Europhysiology 2018.

The four plenary lectures, one chosen by each participating society, provide thought-provoking overviews of physiology, delivered by some of the top leaders in their fields. The Physiological Society is delighted to host it's Annual Review Prize lecture in Berlin, given by David Attwell, University College London whose extensive work on neurovascular interactions and elucidating the roles of pericytes, which he describes as "power switches in the brain" is truly inspirational. We look forward to hearing about his most recent work looking at pericytes in human brain tissue. The Michael de Burgh Daly Prize Lecture will be delivered by Fiona Gribble from the University of Cambridge. Her research determines the actions of gut hormones on target tissues. In understanding how gut hormones are released, they aim to target ways of modulating this release, which may lead to the development of new drugs or diets that treat diabetes and obesity. The third of our prize lectures announced so far is the Bayliss-Starling Prize Lecture given by Maria Fitzgerald, University College London, who is internationally recognised for pioneering work in the basic developmental neurobiology of pain, central processes underlying hyperalgesia and allodynia, and the understanding of pain in infants and children. We also have plenary lectures by Heidi McBride (McGill University, Montreal) on post-translational modification of mitochondrial function and Volker Vallon (University of California, San Diego) on the role of the kidney in the regulation of blood pressure, renal clearance of exogenous and endogenous compounds, and the underlying pathophysiology of the early diabetic kidney. Amongst the keynote lectures, Holger Gerhardt from the Leuven Center for Cancer Biology, Belgium, has a focus on tumour angiogenesis with an aim to consider the refinement of anti-angiogenesis and vessel normalisation therapy. These lectures often provide us with potential new directions or techniques to consider in our own research, regardless of the differences in the organ or system studied. For a full list of all plenary and keynote lectures, visit **europhysiology2020.org**

During the main conference, we have symposia on topics ranging from "The athlete's heart", microbiota, oxygen sensing in health and disease, and the cardiac sodium channel, through to "inhibitory mechanisms in cortical information flow". There are also four focused pre-symposia on cardiac physiology, skeletal muscle, renal physiology and vascular physiology with programmes being finalised as we speak, so do check our website! Two other satellite symposia, sponsored by The Physiological Society have more complete programmes. The first on "Ionotropic glutamate receptors: structure, function and dysfunction" will consider proteins that regulate properties of this family of ligand-gated ion channels and *de novo* mutations in ionotropic glutamate receptor subunits underlying neurological disorders. The second, entitled "Can exercise prevent the age-related decline in adaptive homeostasis? Evidence across organisms and tissues" will bring together leaders in the fields of exercise physiology and ageing research to discuss the current understanding and research gaps in this research. Importantly for our early career physiologists, there will be a dedicated symposium for them, with a programme developed across the societies and relevant to all. We have ensured that there is no clash between subject-specific symposia and this early career symposium so that you can choose to attend both, if you wish. These pre-symposia will take place at the same venue. Registration for all of these is free but you do have to be registered for the main conference to attend and there will be limited spaces, so be sure to register early.

The conference will take place at the Estrel Congress Centre in Berlin from 11 to 13 September 2020, with pre-symposia on 10 September. We look forward to seeing you all in Berlin; we are anticipating a great conference celebrating physiology at its best!

"We look forward to seeing you all in Berlin; we are anticipating a great conference celebrating physiology at its best!"

## Key dates

15 January 2020:
Online registration opens

5 March 2020:
Abstract submission opens

25 May 2020:
Abstract submission closes

15 June 2020:
Early registration closes

15 July 2020:
Late-breaking abstract submission closes (poster only)

1 September 2020:
Late registration closes

10 September 2020:
Pre-Meeting Symposia

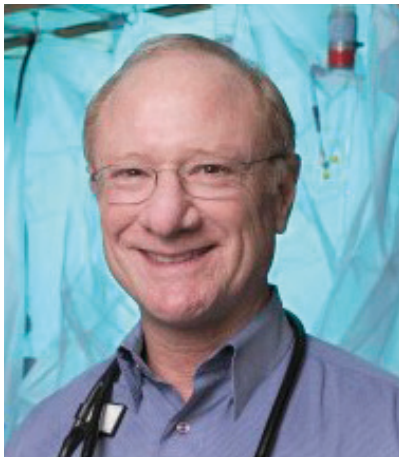
11 – 13 September 2020:
Meeting dates

# Don't lose sight under pressure

## Cranial consequences of a life without gravity

*Justin S Lawley*

University Innsbruck, Austria



*Benjamin D Levine*

Texas Health Presbyterian Dallas, USA

Although humans evolved under the constant weight of Earth's gravity, they appear to be particularly susceptible to changes in gravitational gradients. An example of this is the so-called spaceflight-associated neuro-ocular syndrome, which was first reported in astronauts that experienced impairments in their vision during and after long-duration missions onboard the International Space Station. The symptoms were initially thought to result from intracranial hypertension due to a microgravity-dependent redistribution of fluid volume to the upper parts of the body. While the existence of this syndrome indicates that Earth's gravity field has an important influence on the structure and function of the optic apparatus, it was not until recently that intracranial pressure was experimentally measured during microgravity.

Manned exploration of the galaxy is a dangerous business, not only because of the technical and logistical issues surrounding space travel (to date, all deaths in human space flight have been due to catastrophic loss of the crew vehicle), but due to prolonged exposure to isolation and confinement, hostile and closed environmental conditions, radiation (see Limoli p. 26 and Whittaker p. 36) and importantly the lack of gravity (see Mekjavic p. 30). Life on Mars will no doubt be tenuous, as astronauts will be living in only three-eighths of Earth's gravitational force for many months to years. Thus, a broad scientific understanding of how the human body copes with prolonged periods of reduced gravitational loads will be imperative for mission success.

### How does gravity affect the cardiovascular system?

In the upright posture, gravity acts on the long head-to-foot fluid column ($G_z$) within all three major circulations: arterial, venous and cerebrospinal fluid. For example, arterial blood pressure at the level of the brain is ~80 mmHg, at heart level ~100 mmHg and at the level of the feet ~200 mmHg. In stark contrast, in the supine posture, the effect of gravity is limited to the short chest-to-spine fluid column ($G_x$) with arterial blood pressure being ~100 mmHg at the level of the brain, heart and foot.

These large changes in fluid pressures and subsequent redistribution of fluid volume to the lower extremities makes standing up a challenge to the cardiovascular system most humans do not consider on a daily basis, as complex involuntary reflex adjustments make it possible. Yet, after long-duration space missions or prolonged periods of bedrest, standing up in Earth's gravity is difficult and fainting is common. Thus, physiologists have taken a keen interest in how the human body adapts to both microgravity and bedrest and its implications for blood pressure regulation on Earth (see Norsk p. 40).

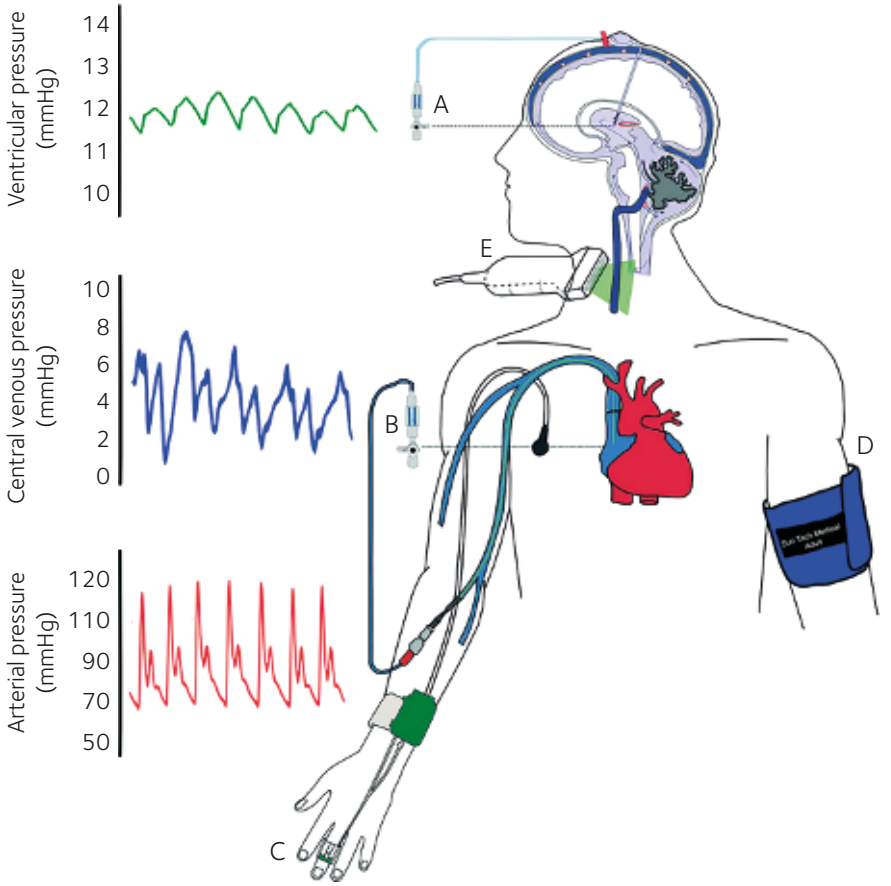



*Figure 1.* Schematic of experimental set-up. Intracranial pressure (A) and central venous pressure (B) were measured directly via fluid coupled pressure transducers connected to the Ommaya reservoir with a butterfly needle and catheter placed in the right atrium, respectively. Additionally, non-invasive measurements of beat-by-beat arterial blood pressure were taken by finger photoplethysmography(C), brachial arterial sphygmomanometry (D) and jugular venous cross-sectional area was assessed by cardiac-gated B mode ultrasonography (E). Note that intracranial, central venous and arterial pressure recordings were referenced to the external auditory meatus and right atrium, respectively (dashed lines). (Taken from Lawley *et al.*, 2017).

"Careful examination of astronauts experiencing neuro-ocular syndrome noted flattening of the eyeball, folds in the choroid, widening of the optic nerve, cotton wool spots on the retina and, in a few cases, swelling of the optic disc"

## Spaceflight associated neuro-ocular syndrome

Careful examination of astronauts experiencing neuro-ocular syndrome noted flattening of the eyeball, folds in the choroid, widening of the optic nerve, cotton wool spots on the retina and, in a few cases, swelling of the optic disc (Mader *et al.*, 2011). These observations, reminiscent of patients with intracranial hypertension (i.e. pathologically high pressure in the brain), alongside the known headward fluid shifts in microgravity, rang alarm bells with concerns of raised intracranial pressure as the underlying mechanism of what was initially termed Visual Impairment Intracranial Pressure (VIIP) syndrome. However, like the great British detective Sherlock Holmes advocates, "*There is nothing more deceptive than an obvious fact*". Thus, the space flight community agreed that only through precise measurements of regional pressures in the human body during both real and simulated microgravity can the pathophysiological role of raised intracranial pressure be substantiated.

## Attacking the problem of accurately measuring regional pressures

Precise measurement of pressure within the human body requires the insertion of a catheter or needle into the fluid compartment of interest. So, measuring pressure inside the brain of healthy volunteers in microgravity is a real challenge! Fortuitously, Benjamin Levine recalled a group of patients from his days as a medical resident whom had an Ommaya reservoir (catheter placed from the lateral ventricle to a reservoir under the scalp) inserted for the delivery of prophylactic central nervous system chemotherapy as part of their treatment for haematologic malignancy. In many of these patients, the reservoir is left in place permanently, even after complete recovery. Intracranial pressure can therefore be measured by placing a small butterfly needle into the reservoir while sutured securely to allow free movement and accurate recordings. For our study we recruited five men and three women with Ommaya reservoirs, and combined measurements of intracranial pressure with central venous and arterial blood pressures, measured at the level of the right atrium of the heart via catheterisation of the brachial vein and determined by non-invasive finger artery photoplethysmography and brachial artery electronic sphygmomanometry, respectively (Fig. 1).

## Quantifying the effect of various changes in gravitational gradients

We set out to answer several fundamental research questions. The first question we asked was simply what happens to intracranial, arterial and venous pressures with normal changes in posture on Earth? The second question we asked was how these regional pressures would be affected by long periods of cephalad fluid shifts with simulated microgravity. The third question was how intracranial, arterial and venous pressures

*Figure 2.* Typical set-up for a participant in a -6° head-down tilt bedrest study. (Image Credit: DLR).

change during freefall-generated acute "microgravity" over the course of a series of earthbound parabolic flights. Furthermore, we wished to assess how these test conditions may be affected by the addition of atmospheric carbon dioxide (0.7%, v/v) and resistance exercise, both of which may increase intracranial pressure on Earth and during microgravity.

While we assessed the first question by asking participants to change posture from sitting upright to lying down while obtaining the relevant measurements, the two other questions required some thoughtful logistics and rehearsal. For example, the second question addressing the effects of protracted cephalad fluid shifts was assessed by placing participants on -6° head-down tilt bedrest for 24 hours to simulate microgravity (Fig. 2). Whereas the third question was much more elaborate, as the participants needed to be secured to avoid free floating during parabolic flight, but no pressure could be applied to the abdomen, as this is known to increase both central venous and intracranial pressures. Moreover, performing resistance exercise without the counter force of gravity is challenging. A typical flight campaign is flown over 4 – 5 consecutive days with one flight per day. Prior to flight, all research equipment needs to be stowed securely and once at a cruising altitude deployed, set-up and calibrated in under a few minutes. With the team at Wyle Laboratories, Inc, we built and set-up the necessary equipment (Fig. 3) and repeated the set-up protocol and measurement procedures in a mock environment for a week prior to each campaign. Staffing each flight typically involved one participant, a study director, an ultrasonographer, a research nurse, a neurosurgeon and a research engineer with a typical participant schedule as follows:

**Day 1**: ~12:00 pm, pick up participant from Houston airport and obtain Ellington airfield badge identification; ~2:00 pm, individualised equipment set-up and subject familiarisation, ~5:00 pm, participant briefing on flight procedures.

**Day 2**: 6:00 am, instrumentation of invasive pressure monitors; 7:00 am, equipment check and calibration; 8:00 am, subject instrumentation with non-invasive devices; 8:30 am, pre-flight and medical briefing; 9:00 am, board plane, take off and data acquisition; 12:00 pm, post-flight debrief; ~1:00 pm, participant tour of Johnson Space Center, thereafter take participant to Houston airport for departure.

## Is pressure in the brain elevated in space? It's all relative

The findings from the first series of studies showed that on Earth, intracranial pressure is high when lying down compared to sitting upright. Thus, pressure in the brain on Earth during a typical day is split into roughly 16 hours in the upright posture where pressure is low and 8 hours in the supine posture during sleep where pressure is "relatively" high. With 24 hours on -6° head-down tilt bedrest, intracranial pressure changed minimally and there was no hint of a progressive rise over time. However, contrary to expectations, when lying down onboard parabolic flight, intracranial pressure actually fell as soon as the flight entered the microgravity phase of each parabola. Yet, although intracranial pressure fell, it did not fall to values observed in the upright posture on Earth. Therefore, when unaffected by Earth's gravity, intracranial pressure is constantly in between the states of upright and supine postures found on Earth. Moreover, independent of gravitational load, exposure to a mild increase in atmospheric carbon dioxide added very little to intracranial pressure, while resistance exercise only transiently elevated intracranial pressure, not dissimilar to that observed on Earth. Ultimately, if we consider a typical 24-hour day on Earth, intracranial pressure is likely *relatively* elevated in space, but pathologically high intracranial pressures, such as those observed in patients with intracranial hypertension, are unlikely (Lawley *et al.*, 2017).

Our findings uncovered the possibility that as human evolution occurred under the constant pull of gravity, and humans habitually spend their waking hours upright with the brain and eyes at the top of a long fluid column, the optical structures and their function may require fluctuations in pressure and volume to operate normally / optimally. However, this

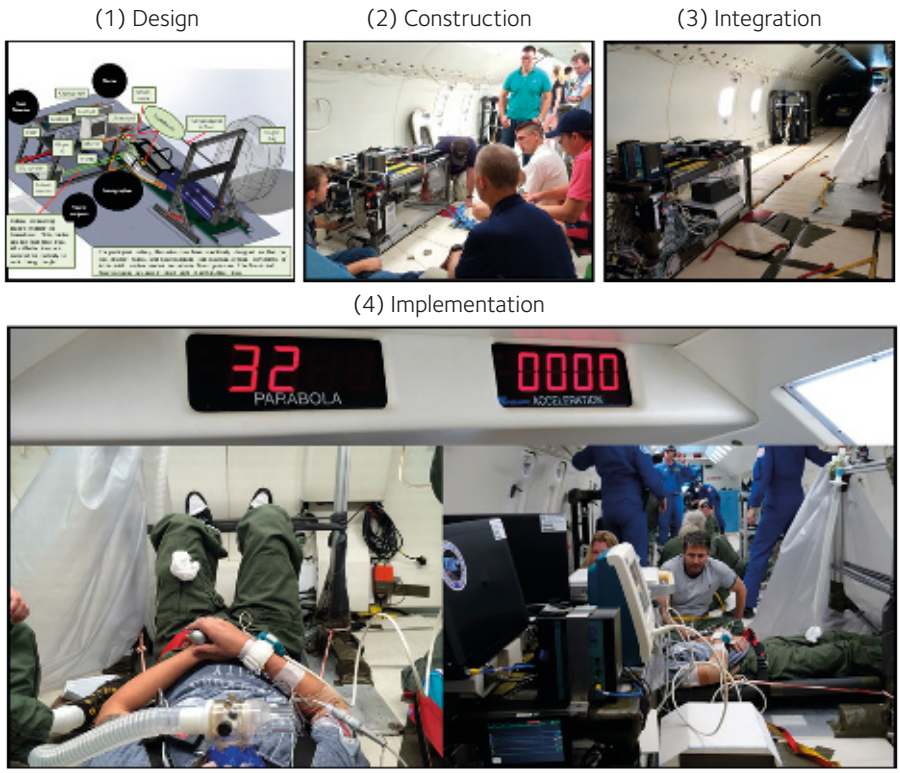



*Figure 3.* Pathway to performing integrative physiological experiments with zero gravity, carbon dioxide inhalation and resistance exercise onboard parabolic flight.

raises a fourth perplexing question: why do participants who take part in long periods of bedrest (up to 60 days) not report changes in their vision, as pressure in the brain would be relatively high and constant for the entire duration? We addressed this question by a keen observation that during previous bedrest studies participants were typically allowed a pillow to aid comfort (Fig 2), which means that while the heart is still -6° below the feet, the head is elevated and experiences relative gravitational effects. We found that wadding even a very small pillow substantially reduces pressure in the brain in the -6° head-down tilt position, therefore providing a simple explanation for the lack of signs and symptoms of space-flight-associated neuro-ocular syndrome in previous bedrest studies. Indeed our observations were later verified by Laurie *et al.* (2019) who showed development of optic disc oedema and increased retinal thickness in subjects after 30 days of strict -6° head-down tilt bedrest without the use of a pillow or repositioning to eat during meals.

## Conclusion

Carrying the great weight of the world often symbolises disadvantageous consequences, but our publication in *The Journal of Physiology* (Lawley *et al.*, 2017) highlights that components of human physiology may actually require the interaction between Earth's gravitational force and habitual changes in posture to function optimally.

Preserving astronauts' visual acuity is an area of considerable concern for long-term space flight (i.e. manned mission to Mars) and a high-priority area of research for many space agencies. Therefore, experimental models of SANS will be important for testing potential countermeasures, as well as investigating the pathophysiology and novel therapies for Earthbound hypertensive and diabetic patients who develop optic disc oedema.

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Justin S Lawley won *The Journal of Physiology* Early Investigator Prize in 2017. See a list of all winners here: **bit.ly/380eWWm**

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"Carrying the great weight of the world often symbolises disadvantageous consequences, but … components of human physiology may actually require the interaction between Earth's gravitational force and habitual changes in posture to function optimally"

# Space brain

## The adverse impact of deep space radiation exposure on the brain

*Charles Limoli*

University of California, USA

Until recently, the effects on the brain of solar and galactic cosmic rays (GCR) at total doses (≤50 cGy) and dose rates (~1 mGy/day) that define the space radiation environment were unknown. Of the wide range of physiological stressors that astronauts would be exposed to during a deep space mission, this is perhaps the most concerning, as these radiation fields possess energies sufficient to penetrate the hull of the spacecraft and tissues of the body, leaving a wake of subcellular damage along the particle trajectories that can compromise the functionality of cells, tissues and organs. Space-relevant radiation exposure to the brain elicits a wide range of behavioral decrements in rodents, and has been shown to occur following a variety of exposure paradigms (radiation types, doses, dose rates) which poses certain concerns to NASA since with our current technology, there is no way to completely protect or shield astronauts from space radiation.

To begin with, significant effort has been devoted to simulating space radiation on Earth, which as one might imagine is not a trivial undertaking. Most of our current knowledge about the biological effects of space radiation exposure have come from studies conducted at the NASA Space Radiation Laboratory (NSRL). The NSRL uses beams of heavy ions extracted from the booster accelerator at Brookhaven National Laboratory (BNL) to simulate exposures to various combinations of cosmic rays (see Whittaker p.36). It is interesting to note how this state-of-the-art facility has evolved over the last 20 years during which time NASA has funded researchers to unravel the various biological consequences of exposure to space radiation. NASA opening the NSRL (circa 2003) that featured a dedicated beam line for radiobiological studies represented a massive step forward for research. At that time, technical capabilities provided for exposures to single ion types at various doses, but capabilities have advanced to allow delivery of combinations of different ions on the same or different days. Another important advancement was the development of a larger, uniform field size that allowed investigators to irradiate greater numbers of experimental models (e.g. cells, tissues, animals) at the same time. Moreover, an enhanced capability to "switch" beam types and energies to provide more realistic simulations of the space radiation environment was also developed. More recently, physicists at BNL have made the necessary advancements to provide a remarkably complex and realistic simulation of GCR; namely, sequential exposure of multiple samples to a complex mixture of 33 beams comprised of multiple ion types and energies. The capability to deliver this

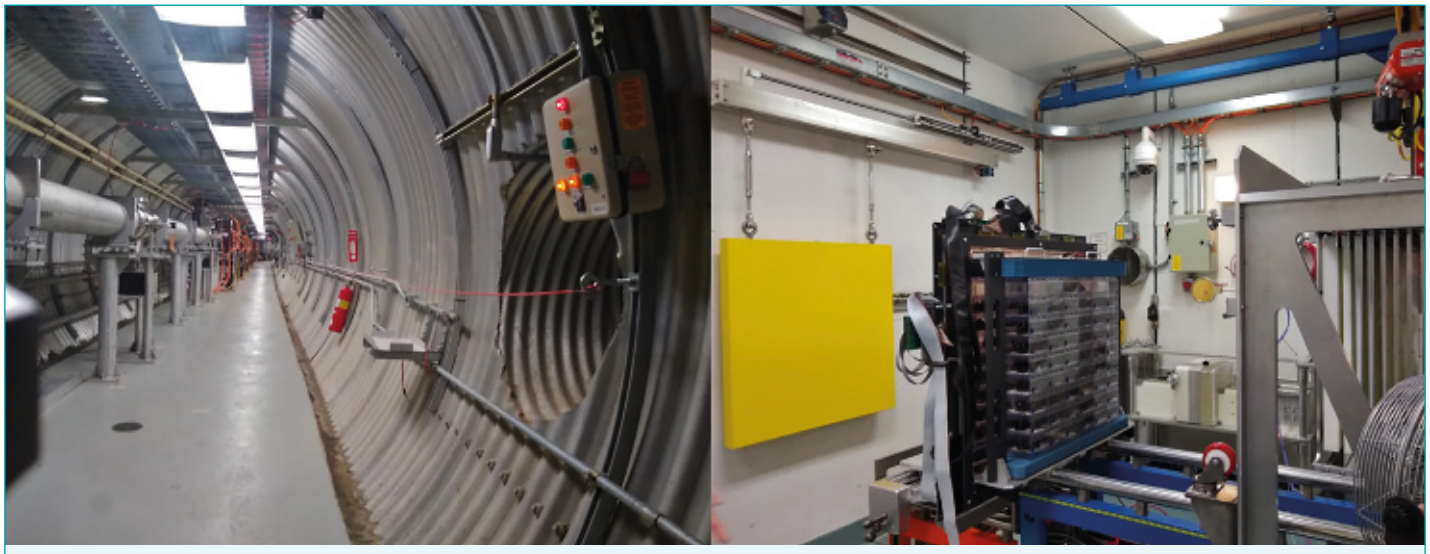

*Figure 1.* The beam line at NASA's Space Radiation Research Laboratory (NSRL). Charged particles travel horizontally within the vacuum tube as they are propelled toward the target area by a series of magnets (left). The target area at the NSRL beam line can be configured to hold a variety of samples including shielding material, tissue culture flasks or animals within holders (shown at right). Upstream magnets and dosimeters provide for beam shaping, beam uniformity and dose quantification.

complex radiation field in a single day or even over weeks provides investigators with an unprecedented tool to determine the effects of the most realistic terrestrial-based GCR simulation available on physiology. Some examples of the NSRL facility and a typical experimental set-up are shown in Fig. 1.

As with most experimental set-ups involving accelerator-based research, operational logistics pose practical limitations that preclude operation of the NSRL around the clock. This necessitated a slightly different approach to more accurately simulate the constant low dose rate environment of space. To this end, a neutron irradiation facility at Colorado State University (CSU) has been built that implements the radioactive isotope $^{252}$Californium ($^{252}$Cf) to allow long-term, chronic exposures at realistic dose rates. In this instance, the experimental setup is rather distinct from that at the NSRL, where the radioactive $^{252}$Cf source is raised and lowered within a lead-shielded compartment to bathe a room with neutron and photon irradiation. Experimental models can be arranged in an annulus around the source at a defined distance that prescribes the desired dose rate. The source is raised while the samples accumulate the desired dose but can be lowered for animal husbandry purposes. With this system, researchers now have at their disposal a new-found capability to expose specimens over the course of several months to low radiation dose rates that simulate many of the dosimetric qualities of the space radiation environment. An example of the neutron irradiation facility at CSU and typical cage arrangement surrounding the $^{252}$Cf source is shown in Fig. 2.

## Behavioural and neurocognitive changes triggered by cosmic radiation

As the use of these highly sophisticated radiation facilities continues, what have scientists learned regarding the consequences of space radiation exposure to the brain? The answer is not good, at least for behavioral performance. Several studies conducted using rodent models over the last decade at BNL and more recently at the CSU neutron facility – implementing single ion, combined ions, or various versions of the most current GCR simulation – uncovered significant radiation-induced deficits in learning, memory and distress behaviors (Parihar *et al.*, 2015, 2016). If the results hold true for humans, which neurocognitive data from the NASA Twins Study indeed suggest may be the case (Garrett-Bakelman *et al.*, 2019; see p. 16), it may influence an astronaut's ability to adapt and respond to unexpected or stressful situations during the near complete autonomy of deep space travel. Clearly, this is an undesired outcome and could jeopardise astronaut safety and mission success.

Radiation-induced cognitive dysfunction has been a bane for clinicians engaged in the radiotherapeutic management of CNS malignancies for decades. While cranial radiotherapy has proven useful for forestalling brain tumor growth, the progressive and debilitating cognitive deficits resulting from such brain tumor treatments have remained an unmet medical need for decades. This reality has foreshadowed many of the findings uncovered by NASA investigators despite much lower total radiation doses and much different radiation types used than that commonplace in clinical practice. Findings from multiple research labs documenting widespread neurocognitive deficits spanning multiple regions of the brain (e.g. hippocampal, medial prefrontal cortex, perirhinal cortex, among others) suggest that whole-body exposures will elicit widespread, network-level disruptions in neurotransmission.

Implementation of a variety of behavioral tasks designed over the years to interrogate the functionality of specific regions of the rodent brain have routinely uncovered cosmic-radiation-induced deficits when compared to similarly treated, yet unexposed, cohorts. As cognitive data sets have accumulated, some surprises have emerged. For one, neurocognitive outcomes measured after a variety of exposure paradigms do not show a strong dependence upon radiation quality, a term that reflects the energy deposition and ionisation pattern that a given type of radiation causes within a cell. Moreover, there are ill-defined dose-responses in the low dose range (≤50 cGy) that would be representative of the accumulated absorbed dose on a mission, for instance, to Mars. Given these low doses, most of the CNS effects are unlikely to result from overt cell death. Cosmic-radiation-induced cognitive dysfunction is also persistent, and shows little signs of improvement, at least over the timeframe of most published studies (3 to 12 months). The lack of dependence on radiation quality and total radiation dose, as well as the persistence of such cognitive deficits found in rodent studies, have brought to question precisely what the critical radiation-sensitive target in the brain is.

"[While] galactic cosmic ray exposure [is thought] to be a significant obstacle to deep space travel, it should not be viewed as a deal breaker for the long-term presence of humans in space"

*Figure 2.* The neutron irradiation facility at CSU. Shown are the annular arrangement of rodent cages around the lead-shielded $^{252}Cf$ source that can be lowered and raised for maintenance and animal husbandry procedures. The arrangement of the cages can be modified to accommodate a variety of samples and configurations, and depending on the actual distance from the source, dose rates can be adjusted accordingly.

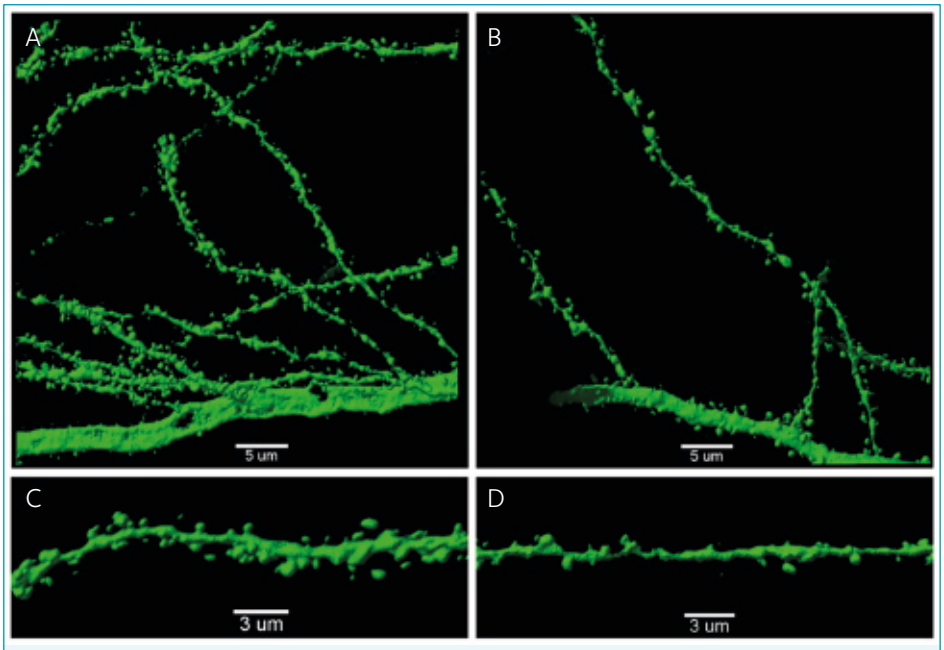


*Figure 3.* Fluorescent images of hippocampal neurons. Dendritic branching in unirradiated controls (A) is more extensive and complex compared to the dendritic structure of neurons subjected to 30 cGy of silicon ions and analysed 1 month following exposure (B). Similarly, higher-magnification images of the dendritic tree reveal that the density of dendritic spines (visualised as protuberances from the dendritic shaft) is much higher in the unirradiated (C) versus irradiated brain (D). Data such as these have revealed that space radiation exposure compromises the structure of neurons at many levels.

## Cosmic radiation-induced structural alterations in the brain

While the foregoing highlights some of the complexities and paradoxes surrounding the functional responses of the space-irradiated brain, or "Space Brain", some hints at the underlying mechanisms have been uncovered. Past work from us and others has found that mature neuronal populations in the brain are subject to radiation-induced structural alterations. Dendrites of many different subclasses of neurons are thin projections that interconnect to other neurons and mediate neurotransmission. Cosmic radiation exposure has been shown to compromise the integrity of these structures leading to marked and persistent reductions in the length, branching and overall complexity of the dendritic tree (Parihar *et al.*, 2015, 2016). Dendritic spines that decorate the length of dendrites represent the structural correlates of learning and memory and contain the synaptic machinery that mediates neurotransmission. Cosmic radiation exposure causes dramatic reductions in dendritic spine density, along with drops in synapse density and axonal myelination – all factors that can compromise neurotransmission and cognition (Parihar *et al.*, 2015, 2016; Dickstein *et al.*, 2018). Examples of some radiation-induced structural changes to neurons are shown in Fig. 3.

Coincident with the structural alterations are increases in neuroinflammation, where cosmic-radiation-induced elevations in microglia serve to perpetuate the footprint of radiation injury in the CNS (Parihar *et al.*, 2016). Activated microglia can actively re-shape and prune the dendritic landscape and trigger inflammatory cascades that disrupt the delicate balance between excitatory and inhibitory signaling in the irradiated brain. The fact that inflammation remains elevated over extended post-irradiation times (≤12 months) suggest this to be contributory if not causal to many of the cognitive decrements observed in rodents exposed to cosmic radiation.

At the electrophysiological level, circuits connecting the neurons into networks have been found to operate less efficiently. Intrinsic cell properties were altered, communication between individual cells was disrupted and memory facilitation along defined networks was impaired, with a collective and adverse impact on neurotransmission at multiple levels (Parihar *et al.*, 2018). Resultant perturbations to oscillatory circuits, broken connections in combination with altered neurotransmitter availability, radiation-induced oxidative stress and changes in lipid oxidation are all additional factors identified by various investigators that could conceivably play significant roles in disrupting electrical communication within the irradiated brain and promoting the onset of cognitive dysfunction.

## Neuroprotection in space?

What recourse does NASA and humanity have in protecting the brain and overall health of astronauts exposed to space radiation? At present, two approaches are the most promising for limiting the adverse health effects of cosmic radiation exposure. The first and perhaps most obvious involves improvements in radiation shielding. While cost and technology limit the payloads we can launch into space, a problem that may in part be resolved by manufacturing and assembling shielding materials in space at orbiting gateways, the fundamental problem remains, namely increasing the number of nuclei in between the cosmos and the body of an astronaut. In the end, this equates to increasing hull thickness and/or redistributing the payload cargo (e.g. instrumentation, food and water) within the ship to provide more optimised regions of minimal radiation exposure. More advanced engineering options are certainly under development of which specialised space helmets may be particularly important for neuroprotection.

The second approach involves identifying pharmacologic/dietary countermeasures for protecting the brain and the rest of the body against radiation-induced normal tissue toxicities. This is a multifaceted approach that is limited in part, as with other aspects of the space program, by practicality and resources. At this juncture, NASA is not in the business of drug development and is better suited to an approach aimed at identifying and/or repurposing an agent already known to be safe and efficacious for an alternative indication. Current research is actively exploring compounds possessing antioxidant, anti-inflammatory and metabolic enhancement properties that have shown some promise in rodent models at reducing radiation-induced complications in the brain and peripheral tissues. Adjusting diets to include foods containing many of the aforementioned properties represents a complementary approach. While further studies are clearly needed, a combination of pharmacologic and/or dietary countermeasures along with enhanced shielding should provide some meaningful mitigation to the radiation problems inherent to deep space travel.

While the work from our laboratory and that of our colleagues implicate GCR exposure to be a significant obstacle to deep space travel, it should not be viewed as a deal breaker for the long-term presence of humans in space (Limoli, 2017). Research identifies risks and uncertainties and provides for contingencies, thereby minimising the adverse impact of unexpected events. While the potential for deep space radiation exposure to compromise neurocognitive functionality presents a concern it also represents a challenge that can be overcome. With proper knowledge, motivation and resource allocation, deep space exploration can be undertaken with acceptable risk. Despite the known and the unknown risks of "Space Brain", humankind will persevere and continue the exploration of the cosmos.

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# May the ($G_z$) force be with you

## Gravity and human space exploration

*Igor Mekjavic*

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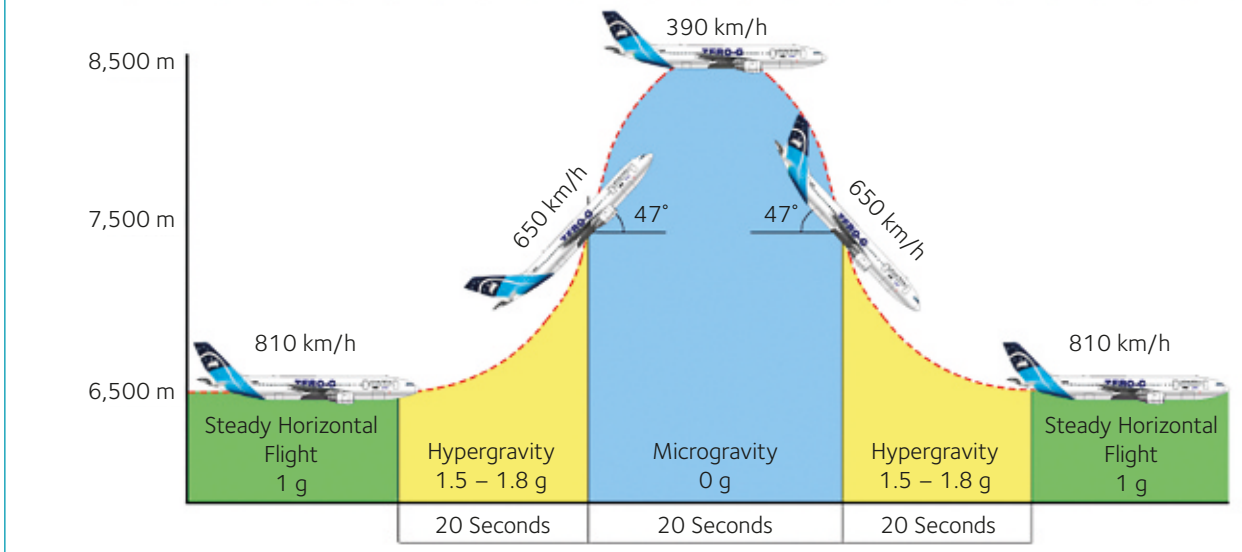
Whether discovering how cells sense oxygen and adapt to its availability (a discovery awarded the 2019 Nobel prize in Physiology or Medicine), or exploring new continents, exploration and discovery are probably among the most exciting human endeavours. How else would Shackleton have assembled a ship's complement for the *Endurance* to explore the Antarctic based on the following advertisement (*Time*, 2003):

*"Men wanted for hazardous journey. Small wages, bitter cold, long months of complete darkness, constant danger, safe return doubtful. Honour and recognition in case of success."*

Since Yuri Gagarin's 108-minute orbital flight in 1961, the investment in space research and technology has allowed us to visit the Moon on several occasions, and in this century to maintain a constant human presence in space aboard one of the most complex structures assembled by an international community of scientists and engineers. This century will witness the establishment of human settlements on the Moon and Mars. The research programme coordinated by the Human and Robotic Exploration section of the European Space Agency explores the many facets of travelling in deep space on human physiological systems. Research in aid of deep space travel and colonisation of Mars should not be viewed from the perspective of the handful of astronauts, who will undertake these missions, but from the potential of harnessing the knowledge to help specific Earth-bound populations. An analogy of the translational nature of life sciences aiding explorers venturing into extreme environments can be found in the work of Scottish physician James Lind (1753), who worked as chief physician of the Royal Naval Hospital at Gosport. He demonstrated that a diet of citrus fruits prevented and cured scurvy, a disease that afflicted sailors exploring the newly discovered continents. His discovery drastically reduced the number of scurvy-associated deaths, not just among the explorers, but also among the general population. Similarly, our current preparations for the exploration of the Moon and Mars can only continue unimpaired with an understanding of the effects of space travel on physiological systems, and with the development of suitable measures and strategies to counter the pathophysiological consequences of prolonged space travel that may ultimately lead to the colonisation of the Moon and Mars.

Withdrawal of the head-to-foot gravitational vector ($G_z$) induces adaptations in all physiological systems (i.e. loss of skeletal muscle mass, bone demineralisation, haemodynamic changes, etc.) (see Norsk p. 40; Rittweger, Frings-Meuthen, 2013; McDonnell *et al.*, 2019). Safe return to Earth's gravitational field relies on the prevention of these potentially harmful adaptations. The initial focus of space physiology research has been understanding



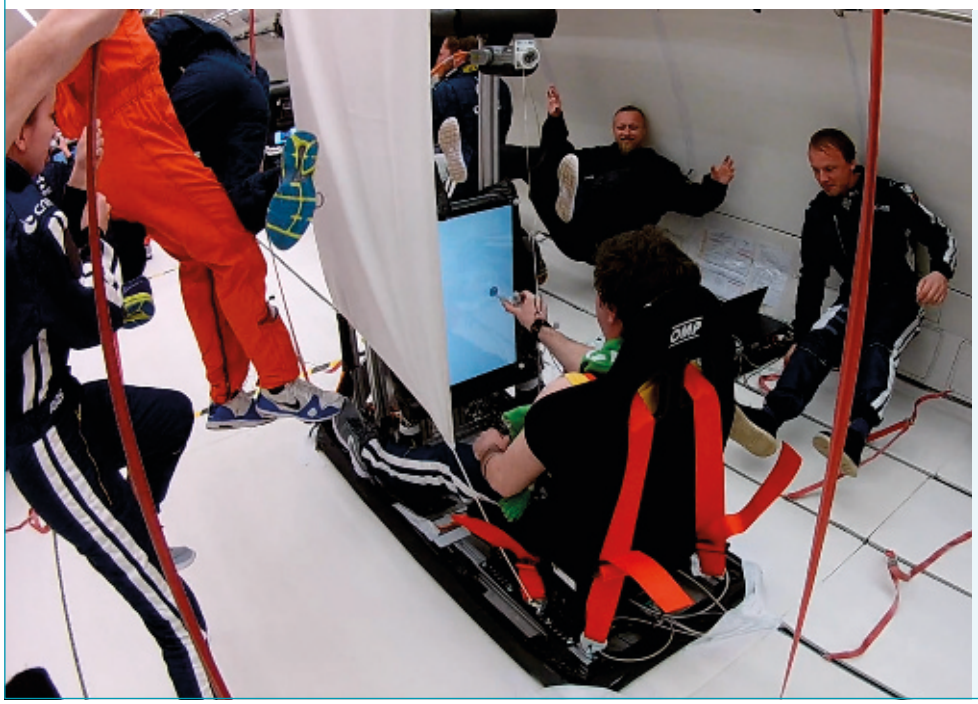



*Figure 1.* Studies during parabolic flight manoeuvres. The upper panel shows the flight pattern of the Airbus during one parabola (photo: ESA). The zenith of the parabola offers 20 seconds of microgravity. The lower panel depicts human motor-control experiments in zero-gravity environment investigating how the brain encodes gravity and how we can prepare astronauts for the challenging environment during and after space flight (photo courtesy ESA). Principal investigator: Jan Babič, Jozef Stefan Institute, Slovenia.

the process of microgravity-induced adaptations, and this has been followed by research investigating mitigating strategies (i.e. exercise, nutrition, etc.). Establishment of a permanent presence on the Moon and Mars will, for logistical reasons, require that the internal environment of habitats be hypobaric and hypoxic (as discussed later in the text). As a consequence, one focus of Space Life Sciences research has been on the effect of hypoxia on the microgravity-induced adaptations observed in normobaric normoxia.

Despite the many countermeasures developed to prevent adaptation to micro- (during space travel and sojourns on the International Space Station) and reduced- (during sojourns on the Moon and Mars) gravity, it is now apparent that intermittent exposure of astronauts to artificial gravity might be the most efficient solution for maintaining their health and well-being, and ensuring a safe return to Earth as suggested by Herman Noordung 90 years ago (Noordung, 1929). Regarding this, the ESA has established a 5-year research programme to investigate the manner in which artificial gravity (using short-arm human centrifuges) can be employed in mitigating maladaptation to microgravity.

## Earth analogues

**Parabolic flights**

Despite the limited opportunities to conduct experiments in space, Space Life Sciences have been able to progress due to the many ground (Earth)-based research facilities that offer valid simulations of the effects of microgravity on human physiological systems. The most well known of these facilities are the parabolic flights (Fig. 1), which offer up to approximately 20 seconds of microgravity (although this varies depending on the flight pattern). The "vomit comet", as it used to be called prior to the introduction of pre-flight anti-motion-sickness medication, conducts parabolas whereby the Airbus "laboratory" ascends from 6,000 m to 8,500 m and back again, conducting this several times in succession. During the zenith of the parabolas passengers experience brief periods of microgravity during which they can conduct their experiments. During the nadirs of the parabolas, there is an increase in the gravitational force. By altering the angle of attack of the flight pattern (i.e. parabolas) the flight can also simulate Mars (38% Earth's gravity) and Moon (17% Earth's gravity) gravity. This may be sufficient to examine some acute effects of microgravity and reduced gravity, but certainly not sufficient to gain insight into the effects of prolonged exposure to microgravity.

*Figure 2.* The Nordic Centre Planica in the Tamar valley (Rateče, Slovenia). The Jozef Stefan Institute Planetary Habitat (PlanHab) Laboratory (ESA ground-based research facility) is located at the Olympic Sport Centre visible in the lower left-hand corner (photo courtesy of the Nordic Centre Planica).

**Bed rest experimental model**

As astronauts continued to extend their sojourns in space, the adaptations to weightlessness became more apparent. As in other extreme environments, such as heat and altitude, all physiological systems were observed to adapt to the 0 G environment, but the kinetics of the adaptation varied. The adaptations to weightlessness were very similar to the adaptations observed in healthy adults rendered inactive and confined to bed for the same duration (Sandler and Vernikos, 1986). Thus was born the bed rest experimental model, which could be used on Earth to study the process of adaptation of physiological systems to microgravity. In these studies, subjects are rendered inactive and their weight-bearing limbs unloaded by confining them to horizontal bed rest for extended periods (up to several months). To increase the fidelity of the Earth-based analogue, and make life more interesting for the subjects, some bed rests are performed with the head in the -6° head-down tilt, as this causes a headward shift of body fluids, giving rise to the appearance of a "puffy face", as seen in astronauts. In Europe, bed rest facilities supported by ESA are the Institut Médecine Physiologie Spatiale – MEDES (Toulouse, France), Deutsches Zentrum für Luft- und Raumfahrt – DLR (Koln, Germany), and Olympic Sport Centre Planica – PlanHab (Rateče, Planica).

**Concordia Antarctic Research Station**

A major issue in spaceflight is the extended confinement in small quarters which need to be shared by the entire crew. Such conditions place a large strain on the psychological status of the crew members. This strain is not so evident in the bed rest models, as there is constant interaction with the medical staff and researchers. As a consequence, ESA has partnered with the Italian (Programma Nazionale di Ricerche in Antartide) and French (Institut polaire français Paul-Émile Victor) research facility Concordia Antarctic Research Station. Scientists now have access to the volunteers within the over-winter crews to study their health and well-being during their one-year assignments at the station.

## Planetary habitats

The Concordia Antarctic Research Station is situated at an altitude of 3,200 m, which introduces the element of hypoxia in all observations. This has proven to be a favourable coincidence, as hypobaric and hypoxic environments are now being considered within future planetary habitats (and possibly vehicles). The main reason for this new strategy in the design of habitats is the concern regarding the potential deleterious effect of frequent decompression procedures required when exiting a normobaric habitat. To prevent decompression sickness during current extravehicular activities (EVAs), as a result of the transfer from the 1 ATA environment of the International Space Station to the pressure within the space suit (about 1/3 of an atmosphere), the astronauts prebreathe oxygen during a slow and gradual decompression, a procedure that requires several hours and the assistance of the remaining crew. This protocol is logistically not practical, and by maintaining a hypobaric environment, the astronauts will be able to transfer from within the habitats to the suit without the need for lengthy and complex decompression procedures. However, hypoxia induced by such a hypobaric environment will be too severe, and the fraction of oxygen may be elevated to prevent the deleterious effects of hypoxia at such a simulated altitude. It is envisaged that the partial pressure of oxygen within the habitats will be equivalent to altitudes between 3,000 m and 4,000 m. As a result of this development, recent research at the Planica facility in Slovenia (Olympic Sport Centre Planica) has focused on the issue of the manner in which hypoxia affects the process of adaptation of physiological systems to bed rest (Fig. 2). To date, all other bed rest studies have been conducted


*Figure 3.* Short-arm human centrifuge to be installed in the Planetary Habitat (PlanHab) Laboratory at the Olympic Sport Centre Planica. Photo courtesy of European Space Agency.

in normoxic environments, whereas the ongoing bed rest studies in Planica have examined these processes in hypoxia. As would be anticipated, there are benefits of adaptation to a hypoxic environment in some responses, and not so in others.

## Countermeasures

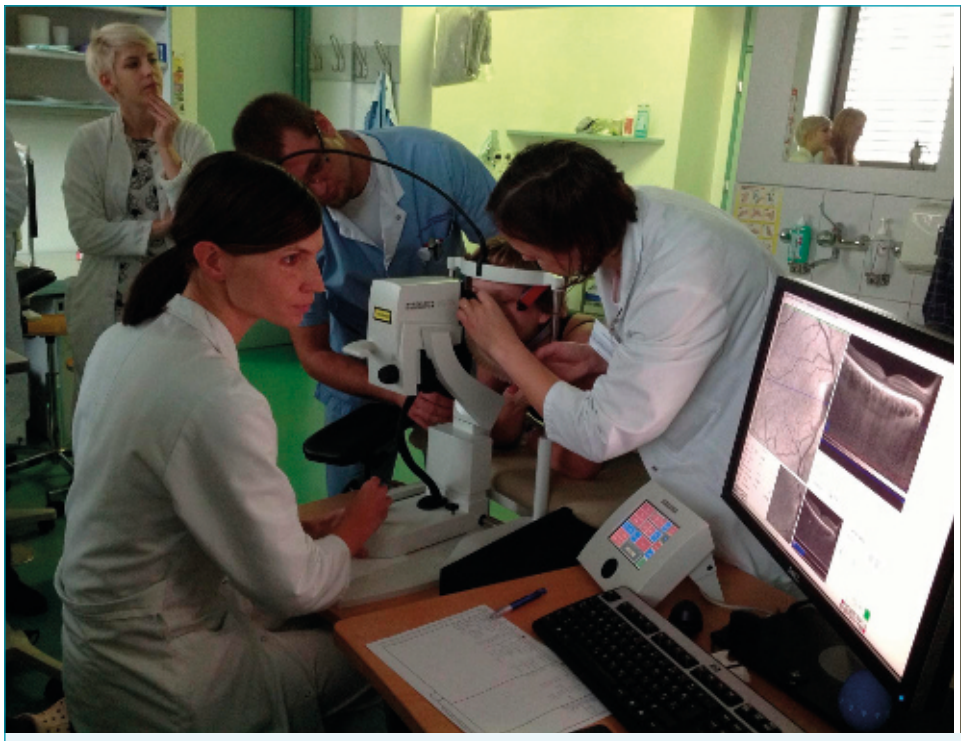
A major cornerstone of Space Life Sciences research is the development and assessment of measures that would counteract the cardiorespiratory, musculoskeletal, neurohumoral, etc., adaptation to microgravity. As a consequence of these efforts resulting from ground-based (bed rest) studies, astronauts have a comprehensive schedule of resistance training and aerobic exercise, coupled with a regulated diet. Despite the relative success of these countermeasures, ESA is considering implementing short-arm human centrifuges on board vehicles on deep space missions to provide astronauts with intermittent and short-term artificial gravity. A programme of research opportunities will be announced by ESA shortly, to focus on the efficacy of artificial gravity, or rather the optimal exposure to a gravitational load in order to prevent the microgravity-induced adaptations. The previously mentioned ESA ground-based facilities in Toulouse (MEDES, France), Koln (DLR; Germany) and Planica (Olympic Sport Centre Planica, Slovenia) will host 60-day bed rests investigating the efficacy of artificial gravity in combination with exercise, nutritional strategies and hypoxia in mitigating inactivity/unloading-induced changes to the physiological systems (Fig. 3).

Of the many factors that influence the health and well-being of astronauts during space travel, and will impact on them during their life on the Moon and Mars, two critical areas remain unresolved. The first is the effect of solar and galactic cosmic radiation (see Limoli p. 26; Whittaker p. 36). This will most likely need to be resolved with appropriate shielding (underground habitats perhaps). The second is the unexplained loss of vision in astronauts exposed to microgravity for prolonged periods, which has been termed Spaceflight-associated neuro-ocular syndrome (SANS) (see Lawley and Levine p. 22). It is most likely attributed to the increase in intracranial pressure, which impacts the intraocular pressure, causing morphological and functional changes in the eye. Ongoing experiments in our laboratory suggest that the resistance exercise coupled with the hypercapnic environment (due to inefficient capacity of the $CO_2$ scrubbers, the fraction of $CO_2$ may be 15 to 20 times that on Earth) of the ISS may contribute to the aetiology of SANS (Fig. 4).

## Life science on Earth for life in space (and on the Moon and Mars)

The principal aim of ESA is to support science in space in support of humans on Earth (Life in Space for life on Earth). However, our research endeavours on Earth are not only crucial for our continued exploration of space, but will also be of relevance to specific populations on Earth.

The current lifestyle of a significant portion of the population in Western societies favours inactivity, which is often coupled with unloading of the lower limbs. The similarity between this and the bed rest exposure is obvious, and the consequences are similar. The difference is that the subjects in bed rest may revert to a more active lifestyle once the experiment is complete. These studies have catalogued the rate of change in the structure and function of physiological systems, and extrapolation of the results to a younger population with inactive lifestyles yields alarming predictions. Based on her experience in coordinating Life Sciences studies at NASA, Joan Vernikos (2011) coined the phrase Gravity deprivation syndrome, to encompass all of the detrimental effects of an inactive lifestyle, resulting in a reduction/elimination of the head-to-foot gravitational force (Gz).



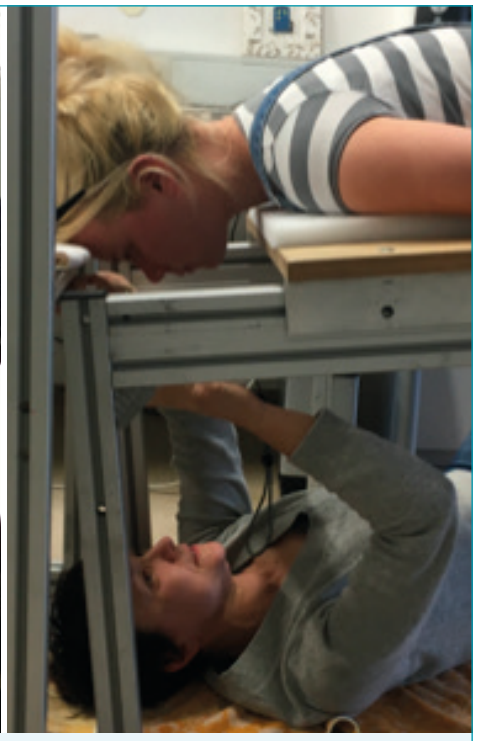


*Figure 4.* Assessment of the separate and combined effects of bed rest, hypoxia and hypercapnia on the retinal layers using optical coherence tomography, OCT (left panel) and intraocular pressure in the prone -6° head-down tilt position (right panel). PI: Polona Jaki Mekjavic, University of Ljubljana Medical Faculty & University Medical Centre Eye Clinic, Slovenia.

Recent bed rest studies confining healthy individuals to inactivity and hypoxia provide insight into illnesses which render the patient similarly inactive and hypoxic, such as chronic obstructive pulmonary disease. The importance of such studies was elegantly summarised by Harriet Tuckey in her biography of her father (Tuckey, 2013), one of the most prominent Extreme Environment physiologists, Griffith Pugh:

*"Lowland people suffering from chronic illnesses such as heart disease, bronchitis, and emphysema lived with long-term deprivation of oxygen. Lacking a comprehensive understanding of what happens to the healthy body when deprived of oxygen over a long period, it was hard for physicians to distinguish which of their symptoms were caused by their bodies adapting – 'acclimatising' – to the shortage of oxygen and which were the direct result of their illnesses. Anaesthetists handling patients in intensive care also required a better understanding of the impact of oxygen lack on the healthy body, as did engineers designing pressurisation and oxygen equipment for high-flying aircraft and space capsules."*

## The physiological aspects of crew selection

We tend to report the physiological responses of subjects exposed to an experimental intervention, such as bed rest, as averages with standard deviations from the mean. A requirement necessitated by the ability to compare the effect of these responses with statistical procedures. "Outliers" and "non-responders" are normally the bane of many theses and reports. Understanding such individual variability in physiological responses has now sparked researchers to gain a better understanding of the magnitude of anticipated variability and the source of such variability (Atkinson and Batterham, 2015). ESA has tasked a consortium of physiologists to investigate individual variability of the physiological responses to bed rest to better understand why some individuals are more resilient to the effect of inactivity/unloading than others[1]. This knowledge will be of benefit in determining crew members for prolonged space flights, since it would allow choosing candidates who would exhibit a lesser degree of musculoskeletal atrophy and cardiovascular deconditioning. This knowledge is the basis of the new field of personalised medicine.

As with the pioneering work of Lind, Space Life Sciences research may be initiated to support human exploration, but the results of the discoveries will aid many Earth-bound populations (particularly those suffering from sarcopenia, osteoporosis, inactivity, hypoxia, etc.). This century will introduce a new era of human space exploration, the success of which will, to a large degree, depend on upcoming generations of physiologists.

[1]ESA Contract No. 4000124642/18/NL/PG/gm: Individual variation in human responses to prolonged bed rest in Slovene bed rest programme.

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# The invisible space killers

## The dangers of space radiation from both inside and outside the solar system

*Ian Whittaker*

Nottingham Trent University, UK

When we talk about dangerous radiation on Earth the public generally think of short-wavelength electromagnetic radiation such as X-rays and gamma rays. While there are many environmental challenges to the physiology of space travellers, the biggest danger comes from ionising high-energy particles which literally "punch" through spacecraft shielding and cause numerous problems for the human body. But where does this radiation come from and how much danger is there?

Even before the advent of the space race, there was interest in exploring far-off worlds. This included an application form for an interplanetary tour reservation in the magazine "Popular Science Monthly" in August 1952. The names and addresses were to be kept on file at Hayden Planetarium ready for the first space trip. The form even had checkboxes for which planets the applicant wanted to visit! Since then there have been visits to the moon in the 1960s and 1970s, and plans to return to the moon in every decade since.

The idea of a human presence on Mars was first suggested by Wernher von Braun in 1948 and has been the goal of space agencies ever since (Zubrin and Baker, 1991; Williamson, 2017). This destination is significantly more difficult to reach than the Moon due to the travel time and increased fuel required. The time factor means that potential Martian visitors spend longer in a very dangerous environment.

The main risk to human health during spaceflight is ionising radiation exposure, which has been well established as a cause of enhancing degenerative tissue defects when leaving the protection of the Earth's atmosphere and magnetic field.

Of course, even without radiation there are multiple challenges to the human body during spaceflight and time off planet, including muscle loss and a decrease in bone density, as well as less obvious stressors such as the change in the day/night cycle and the effect this can have on circadian rhythms. The human body is conditioned to live on Earth well, but in any other environment, pressure and thermal control will be needed to survive. Meaning humans will always have to be enclosed in some way, whether a capsule, base, or spacesuit.

An important first step then is to understand the health risks involved in space travel due to radiation; this will aid in the development of appropriate shielding and allow maximum travel times for future space missions.

### The sun as a source of danger

The sun produces a wide range of electromagnetic radiation with a peak in the visible region (specifically yellow). The short, wavelength emission changes through the solar cycle though; a process in which the sun goes from having a magnetic field like a bar magnet, to having a looped and twisted magnetic field at solar maximum, at roughly five and a half years later. The sun then

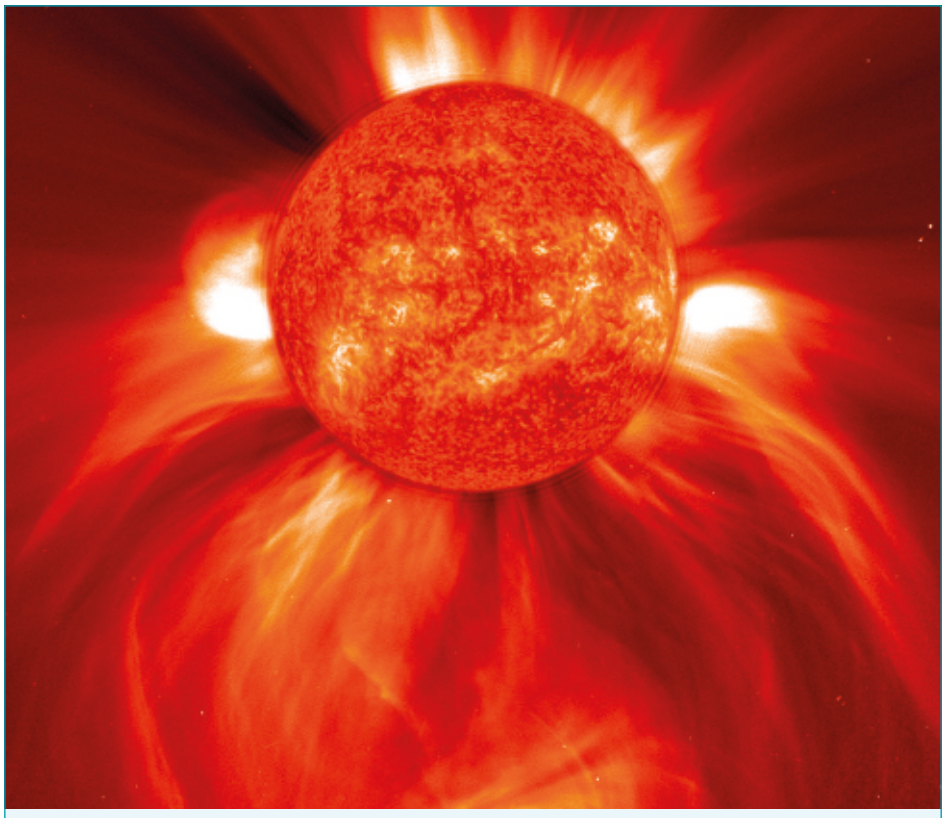

*Figure 1.* An EIT 304 Angstrom and LASCO C2 composite image showing a widely spreading coronal mass ejection as it blasts more than a billion tons of matter out into space at millions of kilometres per hour. [Image Credit: NASA/GSFC/SOHO/ESA].

"A specific proton event in 1972 was calculated to result in absorbed dose rates of 1.4 Gy/h. An astronaut exposed to this event would develop radiation sickness within half an hour of exposure and, probably, neurovascular death within 14 hours of exposure."

returns to the bar magnet configuration over another five and a half years.

At solar maximum, areas of the sun called active regions are observed that build up solar material before ejecting them out into the solar system. Typically, we see this as a solar flare which includes a large burst of X-rays. These flares can produce X-rays up to 10% of the sun's total brightness. While these can vary, an expected radiation dose is roughly 0.05 Gray due to the very short time of the burst of emission (Thirupathaiah *et al.*, 2019), not enough to be imminently lethal on its own.

Far more dangerous are the particles which follow such an event called a coronal mass ejection (CME) (Fig. 1). These are very dense clouds of solar material (primarily hydrogen and helium, but many heavier elements are present too) emitted at the same time as the flare. However, while it takes only a few minutes for the X-rays to reach Earth, the CME takes from two to four days to arrive. The impact of CMEs on Earth have been responsible for massive infrastructure damage due to ground-induced currents. Our ability to predict these types of events are still limited. For instance, an immensely strong CME in 2012 which narrowly missed the Earth was only detected because it hit a near-Earth solar observing satellite (Ngwira *et al.*, 2013). The predicted infrastructure damage if this had been a direct event is estimated to be roughly $2 trillion USD. While these events are rare, they pose a serious risk to humans in space as the Earth's magnetic field is not there to protect them.

A CME can also be accompanied by the emission of highly energetic protons, termed a Solar Proton Event or Solar Particle Event (Fig. 1 and 2). These protons are accelerated up to several GeV (a speed very close to the speed of light), and these events can last from a few hours to several days. A specific proton event in 1972 was calculated to result in absorbed dose rates of 1.4 Gy/h (Parsons and Townsend, 2000). An astronaut exposed to this event would develop radiation sickness within half an hour of exposure and, probably, neurovascular death within 14 hours of exposure.

This is immensely scary as there is very little that astronauts can do to protect themselves. These are directed beams though and – because of the distance from the sun to the Earth – an astronaut would have to be very unlucky to be hit continuously by this form of radiation.

## The Earth surely only protects us?

Another source of ionising radiation is actually generated on the Earth. The Van Allen radiation belts were first discovered in 1958 when the Satellite Explorer 1 was launched (Fig. 3). This satellite had an on-board Geiger counter and was designed to measure cosmic radiation; discovering the radiation belts was a complete accident!

These radiation belts exist because charged particles get trapped within two distinct regions of the Earth's magnetic field at high altitudes, these generally sit at between 700 and 10,000 km above the equator (inner belt) and between 13,000 and 60,000 km above the equator (outer belt) The altitudes are given above the equator as they come closer to the surface at increasing latitude. The outer belt is also significantly more dangerous than the inner belt. As the particles bounce back and forth along the field lines they increase in speed and become dangerous. Solar activity and CME impact can rapidly increase the danger of the radiation belts to astronauts. Especially as high solar activity can move the radiation belts radially inwards and outwards from the Earth, depending on the strength of the solar magnetic field. Normally, these radiation belts produce only the equivalent dose of a medical X-ray for a spacecraft travelling through them in as short a path as possible (on average ~70 mGy a day). The danger comes from either staying too long in one of these belts or travelling during a solar storm. For unmanned high-altitude satellites which orbit through the radiation belts this radiation is mitigated by switching all equipment off and lowering thick shielding to reduce instrument damage.

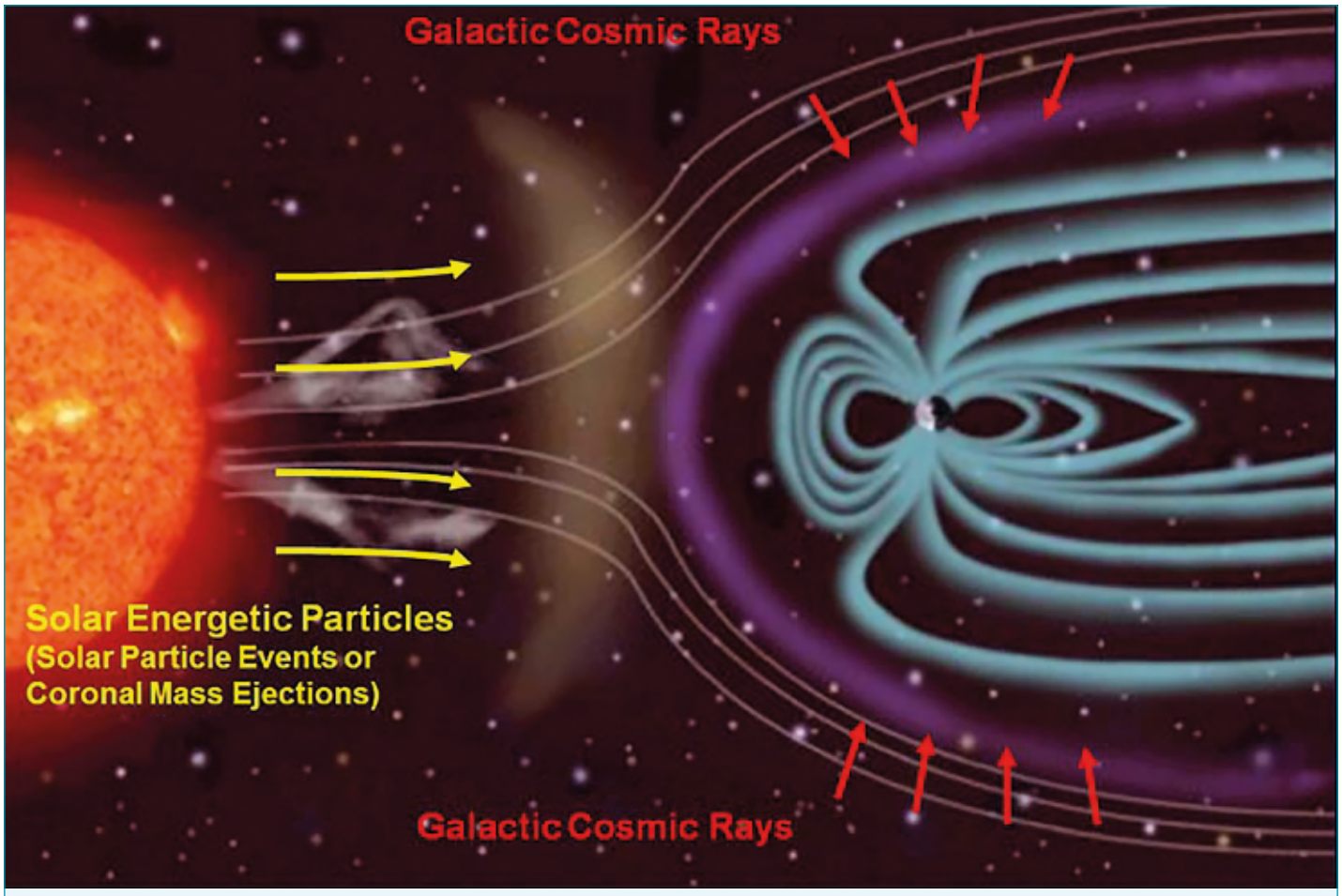


*Figure 2.* Earth's magnetic field (pale blue lines) provides shielding from both the sun and distant cosmic events such as supernova explosions which constantly shower the earth with charged particles, so-called solar energetic particles (grey lines and yellow arrows) and galactic cosmic rays (purple lines and red arrows), respectively. [Image Credit: NASA/JPL-Caltech/SwRI].

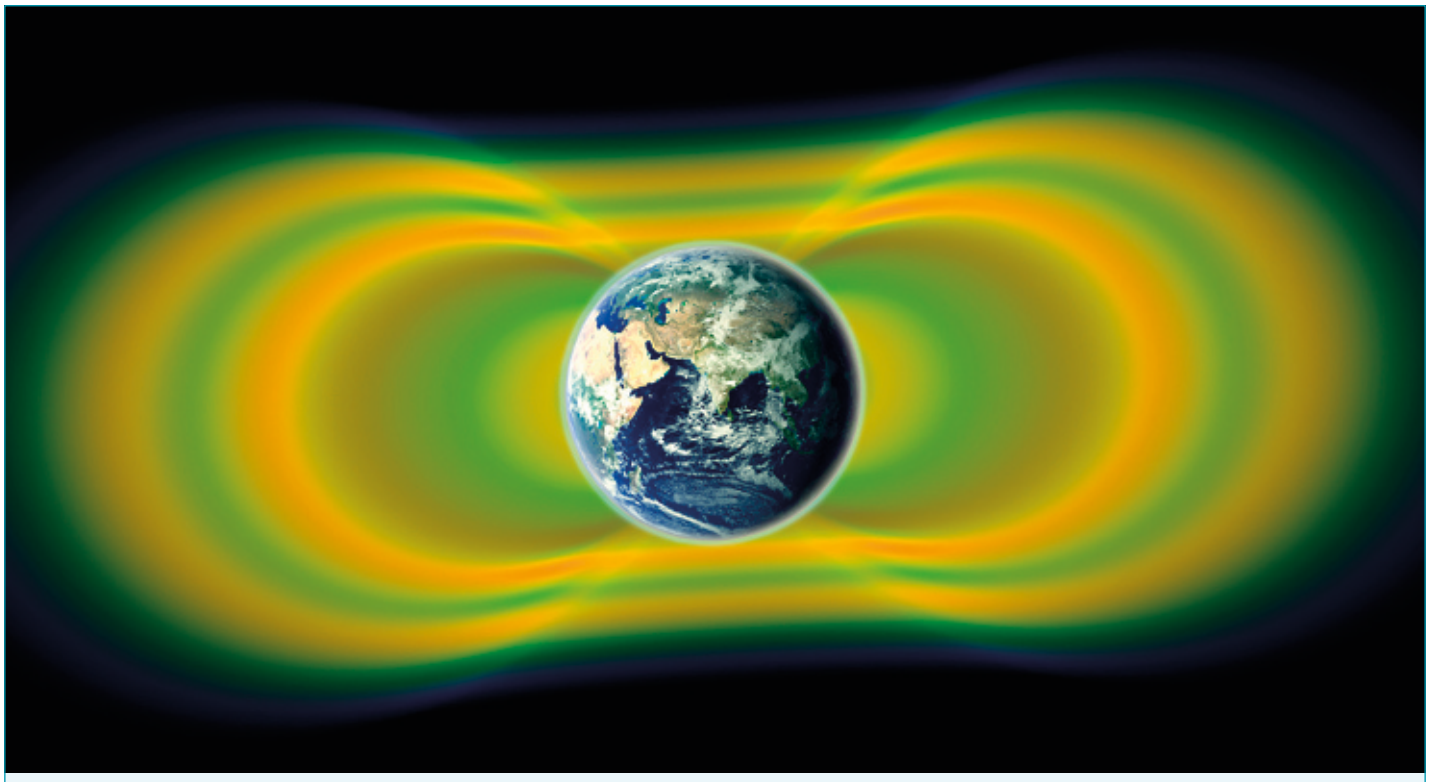

*Figure 3.* The Van Allen Belts are giant swaths of radiation, shown here in yellow, with green representing the spaces between the belts. In 2012, observations from the Van Allen Probes showed that a transient third belt can sometimes appear between the inner and outer belts depending on solar activity. [Image Credit: NASA/Van Allen Probes/Goddard Space Flight Center].

The dangers of the radiation belts were known before the Apollo missions were launched and the mitigation method was to just get through them as fast as possible. There have been near misses. For instance, one of the strongest solar events observed occurred in August 1972 between the launches of Apollo 16 and Apollo 17. If the launch of either had been moved by a few months it could have resulted in a fatal accident. The Apollo 11 capsule returned on 24 July 1969 and the radiation belts had been quiet during the trip; but a geomagnetic storm which occurred only two days later could have given a very different end to the astronauts if they had been delayed at any point in the mission.

## Cosmic rays

Galactic Cosmic Rays (GCR) is the final source of ionising radiation in our solar system, and the only one to originate outside (Fig. 1). GCR are very energetic particles which are thought to be ejected from supernovae and collapsing stars, and consist mostly of protons and alpha particles (which are ionisied helium atoms); the rarer heavier ions are referred to as HZE (literally high [H] atomic [Z] energy [E]) particles, which are heavier high-energy charged elements, moving at relativistic speeds which have been completely ionised.

The rate at which GCR arrive in the solar system also depends on our solar activity. Towards solar maximum, the magnetic fields of the sun flow outwards faster, which acts to deflect GCR away from us and makes the solar system safer. As previously mentioned though, solar maximum is when the most solar energetic particle events occur so there is a risk with whatever part of the solar cycle you choose to travel in.

We are largely protected from the worst effects of GCR by our dense atmosphere on Earth. The discovery of cosmic rays was made in 1912 during a high-altitude balloon flight and ever since then high-altitude balloons have been used to measure the level of GCR. Although, what the balloons are measuring is not in fact the rays themselves but the secondary particles produced when rays interact with the atmosphere. These particles, as they are travelling so fast, actually show evidence of time dilation, where time is moving slower for the particle than the observer (which for physicists such as myself is fascinating).

While we are protected on Earth, there is no such protection in space. The relative vacuum of space compared to the Earth's atmosphere means that any cosmic rays not deflected by the sun's magnetic field at the edge of the solar system will be largely unimpeded from striking a spacecraft. This radiation is also a major concern for lunar landings or permanent bases as the moon has no atmosphere to protect it either.

The risk for astronauts from GCR is a heavily studied topic, and current guidelines suggest that astronauts should not receive more than a 3% lifetime excess risk of cancer mortality. A study by Cucinotta and Durante (2006) gave the percentage of this fatal risk allowance being achieved in different scenarios. In the case of a 180-day lunar mission, the lifetime excess risk from GCR is relatively low at an average 0.7%. In comparison, a Mars exploration mission of 1,000 days (allowing roughly one year on the surface) gave an average risk of 4.6%, suggesting one in every 20 missions could be fatal without protection!

## Mitigating the danger

The best approach to avoiding space radiation is simply to not be there. Travelling to other bodies in the solar system is not a simple concept as straight-line travel is close to impossible. To reach the moon or another planet the most fuel-efficient path involves performing many orbits of varying shape, until the target is reached (known as Hohmann transfers). Any spacecraft starts by orbiting the Earth, requiring no fuel once the orbit is reached, firing rockets at any point turns your orbit more or less elliptical depending on the direction of thrust. The orbit transfer process makes this ellipse large enough to encompass both the Earth and the target then reduce the size of the orbit to only include the target object. This process takes a lot of time; thus, increasing the risk of exposure for anybody onboard.

Shielding is employed in most space missions, but only limited amounts can be installed due to the weight. To reach orbit from a planetary surface using current technology, a rocket has to be mostly fuel with only a very limited weight allowance for the payload (in this case humans and their capsule). This weight budgeting results in most shielding being a thin layer (10s of mm) of aluminium as it is one of the lightest shielding materials available. The thickness of the shielding is the biggest factor in human protection, the ISS shielding blocks a large proportion of the low-energy radiation, although this is because it sits at a very low altitude (~500 km). Still, the personal dosimeters range from 12 to 29 mRads a day.

Thicker shielding can also be problematic though; while it would stop a much higher proportion of low-energy radiation, the high-energy ionising radiation would also start to be absorbed by it. This high-energy radiation is usually travelling fast enough that the probability of interaction is low, when they do hit shielding (or humans), they create dangerous secondary particles.

An alternative to shielding is active magnetic field protection. This may seem like a sci-fi concept but research has been ongoing since the 1960's in this field. The idea of a magnetic shield works well against solar proton events but models suggest it is largely useless against GCR. A design from the late 1970s intended to use a magnetic field to protect against GCR and calculated that the shield would weigh more than 1 million tons, and was 100 m square in size (Paluszek, 1978)! Something largely impractical for a spacecraft but potentially possible for a colonisation attempt.

For short-term missions, the risks to astronauts are relatively low. When we want to explore further afield, the health risk from radiation will increase tremendously. While new solutions are being researched, no specific mitigation method is currently available; the protection of our space explorers should be our primary concern as we move into the era of planetary visits and commercial space flights.

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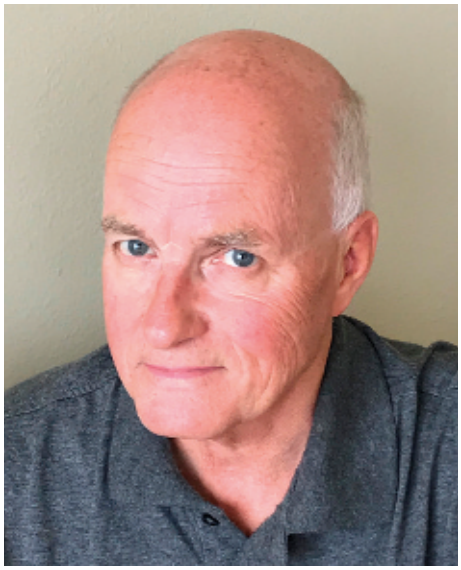
# Getting to the heart of it

## The cardiovascular consequences of spaceflight



*Peter Norsk*

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Human spaceflight started 58 years ago with the launch of the Russian cosmonaut, Yuri Gagarin, who completed one orbit around Earth on 12 April 1961. Eight years later, 50 years ago, NASA landed the first humans, Neil Armstrong and Edwin (Buzz) Aldrin, on the lunar surface with Apollo 11. Since then, the longest human mission in space is 438 days on board the Russian Space Station, Mir, by Valery Polyakov in 1995. As of today, 574 humans have visited space. The return journey to Mars from Earth will take 1,000 days, and there are several physiological challenges to overcome in bringing humans safely back to Earth.

One is managing the shift of blood and fluid into the heart and head that occurs during weightlessness and ensuring that no harm will occur to central nervous function and the cardiovascular system. Another is maintaining adequate muscle and bone strength by efficient exercise prescriptions with specialised equipment, designed to fit into small vehicles and habitats. Another concern is maintaining an efficient immune system and supplying the crews with sufficiently nutritious and palatable food. Finally, it is a challenge to protect astronauts against the long-term effects of space radiation, particularly the effect on brain function and the cardiovascular system.

### Pumping blood in a weightless environment

My space research career started in August of 1978. Before that, I had been fascinated by the Apollo program and as a high school student during the Moon landings, I knew all the details of the missions. This fostered an interest in combining my medical studies with spaceflight health issues, and in 1978 I became a student fellow in a Danish space physiological research group using a national grant to support scientists, who participated in the human spaceflight programs of the European Space Agency (ESA). We specialised in how the cardiovascular system and the associated regulation of fluid and electrolyte balance adapts to weightlessness in space.

A prominent problem was – and still is – the magnitude of the headward blood and fluid shift that occurs because of weightlessness (0 G), where no gravitationally induced hydrostatic pressure gradients exist. In 1993, we aimed to estimate the change in central venous pressure (CVP) in one astronaut before, during and a couple of hours after launch into space in the Space Shuttle to estimate the increase in cardiac preload caused by the fluid shift. In two previous Space Shuttle missions, a US team had observed – much to their and our surprise – that CVP in three astronauts decreased in space compared to in the supine body position on the ground (Buckey *et al.,* 1996). We observed the same decrease (Foldager *et al.,* 1996). This was surprising, because the expectation had been that the fluid shift in weightlessness would induce an increase in CVP to somewhat above that of being 1

*Figure 1.* Parabolic flight in a Caravel in France in 1991, during which we measured central venous pressure invasively in eight subjects during short periods (20 s) of weightlessness (Videbaek and Norsk, 1997). The aircraft followed a Keplerian trajectory, whereby a free-fall condition (0 G) was created symmetrically around the top. The 0 G phase was preceded by 20 seconds of pulling up to 2 G and then again followed by an up to 2 G descending phase of similar duration.

G supine. In both cases, CVP was measured through invasive catheters fed into the superior vena cava through a cubital vein either with a fluid-filled system connected to a transducer outside the body (Buckey *et al.,* 1996) or with a transducer at the catheter tip (Foldager *et al.,* 1996).

Shortly thereafter, we (Videbaek and Norsk, 1997) repeated the measurements in eight subjects during 20 seconds of 0 G during parabolic flights (Fig. 1). Buckey *et al.* (1996) had also observed in their three astronauts that even though CVP decreased in space, left ventricular end diastolic volume as estimated by echocardiography increased; a paradoxical result. However, our parabolic flight data revealed the same, but we also measured oesophageal pressure through a balloon-tipped air-filled tube positioned via the nasal cavity, down the oesophagus to lodge behind the heart. Simultaneously with the decrease in CVP, we observed an even greater decrease in oesophageal pressure indicating that 0 G expands the thoracic cage compared to being 1 G supine. This mechanical expansion dilates the heart and increases transmural CVP. Cardiac preload therefore increases in weightlessness as a combination of an expansion of the thorax and the head-ward fluid shift (Videbaek and Norsk, 1997).

According to Starling's law of the heart (Patterson and Starling, 1914) an increase in cardiac preload induces an increase in stroke volume and thus cardiac output, a phenomenon that also occurs in space. We observed in an investigation on the Space Shuttle in 2003 an increase in stroke volume and cardiac output of 22% (Norsk *et al.,* 2006) a week into the flight. Later on the International Space Station, we found even more pronounced increases of 35 – 41% (Norsk *et al.,* 2015) between three and six months of flight. Thus, stroke volume and cardiac output increase more during long-duration flights than short. The same foreign gas rebreathing technique for both space missions for estimating cardiac output was used (Clemensen *et al.*, 1994; Gabrielsen *et al.*, 2002). The reason for the more pronounced increase in stroke volume and cardiac output during longer missions versus shorter is not clear at present but could be because of the efficient cardiovascular effects of the physical exercise on the International Space Station (Hughson *et al.,* 2012).

At the same time as cardiac output is increased by 0 G in space, systolic, diastolic and mean arterial pressures decrease by some 10 mm Hg (Shykoff *et al.*, 1996; Baevsky *et al.*, 2007; Norsk *et al.*, 2015). Thus, systemic vascular resistance decreases (calculated as mean arterial pressure divided by cardiac output) (Shykoff *et al.*, 1996; Norsk *et al.*, 2015). The mechanism for the decrease in systemic vascular resistance, which is indicative of peripheral arterial vasodilation, is currently unknown, because sympathetic nervous activity is maintained in space at the same level as being seated upright on the ground (Norsk *et al.,* 2015; Fig. 2). A suppression of the efferent sympathetic nervous activity is therefore not the mechanism for the decrease in systemic vascular resistance.

To identify the mechanisms of the blood pressure reduction and peripheral vasodilatation in space is one of the challenges for the future.

"Physiologists are most concerned about the combined effects of weightlessness and space radiation on the central nervous, ocular, cardiovascular, sensorimotor and immune systems"

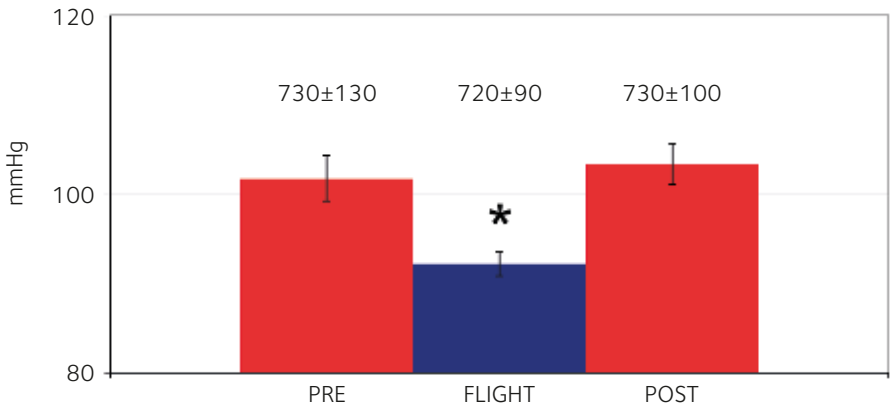


*Figure 2.* The numbers at the top indicate plasma concentration of noradrenaline (ng/L, mean ± SEM) in cubital venous blood sampled in seated ($n$ = 8) astronauts before (Pre), three to six months during (Flight) and two months after (Post) spaceflight on the International Space Station. The columns represent ambulatory mean arterial pressures as averages (± SEM) over 24-h periods around the same time as noradrenaline was sampled (Norsk *et al.*, 2015). As can be seen, venous plasma noradrenaline was unchanged in space in comparison to the seated posture in 1 G, whereas blood pressure decreased significantly (*, p = 0.006). Thus, the efferent sympathetic nervous system does not seem to be a mediator of the decrease in blood pressure in space.

## Spaceflight-associated neuro-ocular syndrome (SANS)

More than 10 years ago, astronauts started to report occurrences of vision changes in space. They were mostly of refractory character and corrected for by adjustable glasses (Stenger *et al.*, 2017). NASA flight surgeons started to monitor other ocular variables such as retinal changes by fundoscopy, which in some cases indicated disc oedema. By using optical coherence tomography (OCT) and ultrasound imaging, more details have later been obtained, and choroidal folds, cotton wool spots, increases in optic nerve sheath diameter and globe flattening have also been detected (Mader *et al.*, 2011; Stenger *et al.*, 2017). Collectively, one or more of these manifestations constitute what is called SANS. Recent data have revealed that disc oedema is preceded by gradual increases in retinal thickness. Laurie *et al.* (2019) were able to induce some of these changes during strict, 30 days of six degrees head-down tilted bed rest, which indicates that the shift of blood and fluid to the head is a pivotal mechanism. It appears that some astronauts are more sensitive to SANS than others, indicating that there maybe a genetic disposition to this syndrome (Smith and Zwart, 2018).

SANS is one of the highest prioritised health risks of long-duration spaceflight, and much research is initiated by the space agencies to understand the details of the mechanisms of the syndrome and how to counteract it during, for example, a three-year mission to Mars.

In addition to SANS, concerns also exist regarding possible impacts of spaceflight on not only the ocular but also the central nervous system. Structural changes by magnetic resonance imaging of the brain in the days following landing from the International Space Station have been detected (Roberts *et al.*, 2018). Whether they have any clinical health or functional impacts are unknown at present.

## Cardiovascular remodelling in spaceflight

Results of ground-based rodent studies have indicated that changing the pressure distribution by shifting blood and fluid to or away from the head by body tilts induces changes in the structure of the arterial walls (Zhang, 2013). Thickening of arterial walls is also evident in hypertension, for example (Mulvany, 2012). Data from two studies on the International Space Station indicate that the carotid artery increases in stiffness during and immediately following spaceflight (Hughson *et al.*, 2016; Arbeille *et al.*, 2017). In one astronaut with almost one year in space on the International Space Station (340 days), carotid wall thickness increased as well as biomarkers indicating increased inflammation and oxidative stress in the cardiovascular system (Garrett-Bakelman FE *et al.*, 2019). Thus, there are some indications that the carotid arterial wall structure may change during long-duration spaceflight. The clinical implications of these observations are, however, currently unknown.

## Other physiological effects

In 2011, I joined NASA as a contractor to lead the physiological research in the Human Research Program. At that time, I had been mostly involved in cardiovascular and fluid volume regulation research concerning spaceflight. Thus, I had to understand the status of other physiological areas concerning effects of long-duration flights.

Apart from the cardiovascular system, the main areas of concern are the ocular, central nervous, sensorimotor, immune and musculoskeletal systems and to determine the most efficient nutritional composition of the food systems to maintain astronaut health and performance during long-duration missions. Regarding the musculoskeletal system, maintaining muscle strength for performance of the required mission tasks is important, as is maintaining sufficient bone strength to avoid an increased risk of fracture due to bone demineralisation. The key countermeasure against these effects is regular resistance exercise. The future challenge is to develop an exercise device that can be accommodated in a small space vehicle or a habitat and still be able to fulfill the musculoskeletal and aerobic requirements (Ploutz-Snyder *et al.*, 2014). SANS is of particular concern, as well as whether brain function is affected (Mader *et al.*, 2011; Stenger *et al.*, 2017).

We know how weightlessness affects the sensorimotor system, and that all astronauts experience balance problems immediately after landing (Mulavara *et al.*, 2018). This is of concern after landing on Mars, where the key question is, how long after landing will it take the astronauts to recover and be able to perform the required mission tasks? The immune system is attenuated by spaceflight, leading in some cases to viral reactivations and rashes, and major efforts are directed towards a host of protective interventions, mainly to decrease operational stress and supply foods with antioxidants (Crucian *et al.*, 2018). Finally, defining the optimal food composition as well as identifying which food items are most applicable for physiological health protection is a challenge (Smith and Zwart, 2018).

## Future plans for deep space missions

NASA is currently planning for future human deep space missions beyond the van Allen Belts with the so-called Gateway project. The plans concern regular human missions to a small habitat orbiting the Moon. The idea is to have a crew of four visit the habitat for some 45 – 60 days on an annual basis with gradual increases in durations as a human test bed for understanding the impacts of the deep space environment on human physiology. The plans now also include landing astronauts from the Gateway habitat to the surface of the Moon, with the first mission to land a female astronaut in 2024.

It is of high priority to understand the combined effects of weightlessness and deep space radiation on oxidative stress and cellular damage, and how this impacts health and performance. Currently, only 24 astronauts, as part of the Apollo program (1968 – 1972), have been in deep space and only for a maximum of 12 days. Therefore, very little is known regarding the physiological effects of long-duration exposures to the deep space environment.

## Conclusion

Surprises and paradoxes concerning how the cardiovascular system adapts to spaceflight defy explanation, for example mean arterial pressure and systemic vascular resistance decrease during months of spaceflight despite an unchanged efferent sympathetic nervous tone. For future deep space missions, to the Moon in the 2020s and to Mars in the 2030s, physiologists are most concerned about the combined effects of weightlessness and space radiation on the central nervous, ocular, cardiovascular, sensorimotor and immune systems, and these will be the focus of intense research in the coming years.

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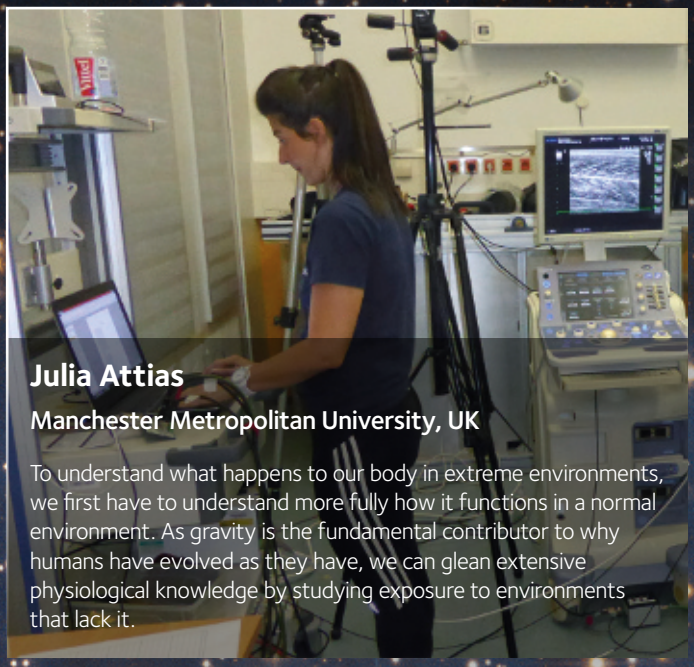
# Why research space physiology?

We asked space physiologists around the world to tell us about their research, and what inspired them to pursue research into the worlds beyond our own.



## Julia Attias

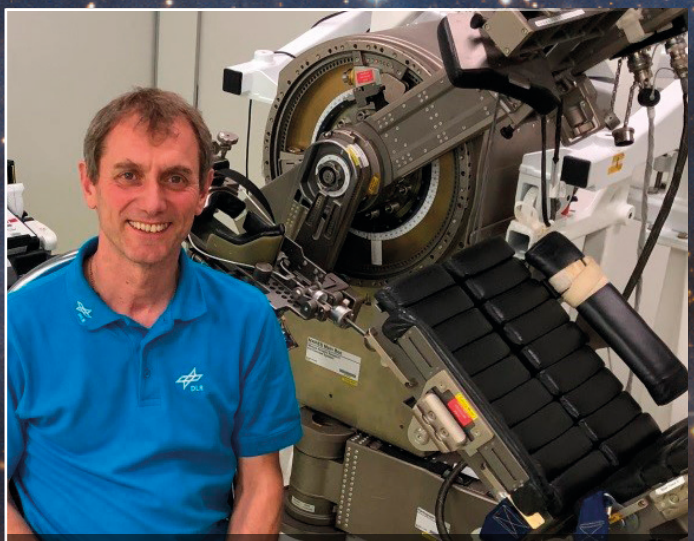
**Manchester Metropolitan University, UK**

To understand what happens to our body in extreme environments, we first have to understand more fully how it functions in a normal environment. As gravity is the fundamental contributor to why humans have evolved as they have, we can glean extensive physiological knowledge by studying exposure to environments that lack it.

## Carsten Lundby

**Lillehammer University College, Storhove, Norway**

I have for a long time been interested in how physical exercise and inactivity affect human physiology, and specifically studying the latter in space. Our long-term goal is to quantify blood volume in space. In my opinion, this is a much overlooked factor that may prove important to monitor during prolonged missions to for example Mars. We have developed an automated blood volume analyser – the Detalo Performance – and thus far have tested our equipment during parabolic flights that deemed our device as effective for our mission.



## Jörn Rittweger

**German Aerospace Center (DLR), Cologne, Germany**

Space physiology fascinates me for several reasons: its foundation on science and engineering, the opportunity to study organismic responses to extreme challenges, and not least the opportunity for discoveries that matter to medicine on Earth. For example, we found in bed rest studies (a ground-based model of microgravity) that resistive vibration exercise can prevent muscle wasting and bone loss. This is not as trivial as one might think, as the effort required for preservation is much greater in bed and in space than in a normal 1 G environment. Strangely, the countermeasure is not based on suppressing exaggerated bone resorption, but rather by fostering bone formation to match the resorptive boost.

## Derek O'Keefe

**NUI Galway, Galway, Ireland**

A Martian day (referred to as a sol) lasts 24.65 h rather than the 24 h day on Earth. As part of a team, I carried out an experiment on sleep disruption and sleep deprivation in a Martian analogue base in the high arctic, where there is continuous sunlight. Our summary thoughts were that while subjective data demonstrate improved sleep and alertness during the sol, objective data demonstrate no significant alteration of sleep patterns. Importantly there was no apparent cognitive decline over the course of the mission.


## Damian Bailey

**University of South Wales, Pontypridd, UK**

Astronauts returning from long-term spaceflight encounter a variety of health problems that are similar to those found in the elderly (accelerated ageing). Spaceflight-associated neuro-ocular syndrome (SANS), related to a build-up of pressure inside the brain, is considered the top health risk for long-duration spaceflight. Our research is the first to demonstrate that gravitational transitions result in a minor opening of the blood-brain barrier due to the combined effects of increased blood flow especially to the back of the brain and the formation of free radicals, invisible molecules floating around the blood stream.

## Lonnie Petersen

**University of California San Diego, San Diego, USA**

I am fascinated by space as a scientific platform which allows us to generate knowledge about human physiology we could not learn in other ways. Through our efforts to develop and test counter-measures to reduce pressure and volume overload in the brain of astronauts during long-term spaceflight, we have also uncovered the significant clinical potential of the same intervention for patients on Earth with disrupted brain pressure regulation, such as following head trauma or stroke. The aim of my work is to maintain human health during exploration class missions, but I am equally excited about the spin-down applications which really increases my target patient population from a select few space-travelers to include millions of patients here on Earth.

## Thu Jennifer Ngo-Anh

**European Space Agency (ESA), Netherlands**

I have both a medical and a neuroscience background; understanding how the body, and specifically brain, works has always interested me. Space is the most extreme environment one can think of; studying the changes that the body and mind go through when exposed to the space environment is therefore extremely fascinating. What I find most striking is to see how the human body is able to adapt very quickly and efficiently to all the changes caused by the space environment. There has not been a single crewmember who has not adapted to microgravity and space conditions! Understanding what happens and identifying countermeasures to mitigate those risks and changes is something that is not only relevant for enabling future safe and sustainable missions into deep space, but also has very practical applications for life on Earth. In addition, we have and will learn a lot about ourselves! I am convinced we will continue to do so with the human spaceflight activities that are in the works.

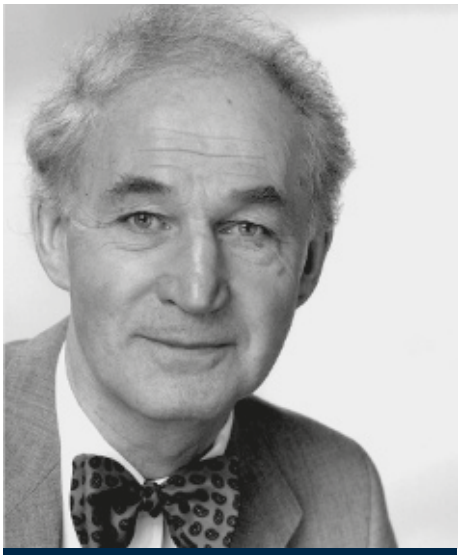
## Adam McDonnell

**Institute Jozef Stefan, Ljubljana, Slovenia**

I've always been interested in extreme human performance. When I was younger I read essentially any book I could about the first polar explorers which seemed remote and I suppose at the time almost as isolating as spacefarers. Quite fascinatingly, more people have been to space now than have circumnavigated the globe solo by sail. When I was a teenager and then in college I was drawn to Olympic athletes and to the feats they could perform. But it was in my final year I started to realise that the human race survived by a collective ability to perform and explore rather than by advances of any one very talented individual. This is where my love for understanding how humans as a species perform in adverse environments came from. The space aspect slowly grew on me from there and I've spent the last 13 years investigating space life science and its translational role to earth.

Image credit: NASA

# Obituary: William Stanley Peart 1922 – 2019



Stanley Peart

Amongst the great British clinician scientists of the twentieth century, Stanley Peart was a giant. His international fame was based on his remarkable scientific research on the autonomic nervous system and the renin-angiotensin system – two systems that play a vital role in the regulation of the circulation and the kidney.

Born in South Shields, County Durham, Peart was a Tynesider. The family moved several times during his childhood and eventually to London. At King's College School Wimbledon, he excelled in the sciences and entered St Mary's Hospital Medical School with a scholarship in 1938. A year later, with the outbreak of World War Two he was persuaded to continue his medical studies. By 1943, as a house physician he was advised by his mentor, George Pickering, to spend a short time in the laboratory of Alexander Fleming. This was Peart's first exposure to research.

At the end of his house jobs, Peart applied for a Medical Research Council (MRC) studentship to work with John Gaddum in Edinburgh in 1946. Gaddum was a shy, gangling figure, awkward in conversation, but a superb mentor. Peart was challenged to work on sympathin, a substance putatively released from sympathetic nerves. There was uncertainty as to whether this was adrenaline or some other mediator. The question was "what actually is released from the nerve endings and how could you measure it?" Peart realised that, rather than the ewe's liver, then used, a much better experimental model was the perfused spleen, with a rabbit ear as the bioassay for the vasoconstrictor effects of the effluent from the spleen. After a series of painstaking experiments, he realised the nature of splenic sympathin could not be adrenaline but was noradrenaline. This result published in *The Journal of Physiology* in 1949.

By 1952, Pickering was convinced that the future of hypertension research involved the identification of components of the renin-angiotensin aldosterone system (RAAS). The technology to investigate the RAAS was not available in the laboratories at Mary's and Peart moved his work to the MRC laboratories at Mill Hill. The challenge was to purify and identify the nature of the blood-pressure-raising substance, angiotensin. His early work involved the development of reverse-phase chromatography and the ultimate identification by electrophoresis and spectrophotometry of the amino acid sequence of the decapeptide angiotensin 1. In collaboration with Don Elliott, the resulting classic paper was published in *Nature* in 1956.

> "His early work involved the development of reverse-phase chromatography and the ultimate identification by electrophoresis and spectrophotometry of the amino acid sequence of the decapeptide angiotensin 1"

Peart left Mill Hill in 1954 to return to the Medical Unit at St Mary's, where he was invited to apply for Pickering's Chair. The youngest applicant by far, he was appointed to the post. The St Mary's Unit had evolved under Pickering's influence into the field of hypertension with a focus on how the renin-angiotensin aldosterone system actually worked. The Swiss pharma company Ciba had synthesised angiotensin and this was used for exploratory studies in the laboratory to establish its actions. The interests of the team widened, influenced by Roy Calne, a future internationally renowned transplant surgeon. The team had the experience and ability to start renal transplantation. This was no doubt stimulated by the recent availability of the immunosuppressive agent, azathioprine.

Hypertension in the early 60s was considered the poor relation of cardiology and, in contrast to the enormous national and international cardiology meetings, a small International Hypertension Group of no more than 50 participants held its first meeting in northern Italy. This embryonic hypertension club has now evolved into an International Society with over 4,000 members.

During the 70s and 80s, Peart chaired the Medical Research Society, a society which was probably responsible for the development of academic medicine in Britain. He was appointed to the board of the MRC. He also became a Wellcome Trust trustee. By today's standards, the Trust was then extremely small with a limited budget of around £1.5 million per year.

After being elected a Fellow of the Royal Society in 1969 and knighted in 1985 for his contribution to medicine, Peart retired in 1987. This allowed more time for a passion for opera. He loved the blood and thunder operas – those with manifestly aggressive actors and singers – Don Giovanni and Tosca were his favourites. With Italy in mind, a Festschrift (a collection of writings in honour of a scholar) was arranged for him in his favourite place on the banks of Lake Como. It was a memorable occasion attended by over 100 of his former friends and colleagues.

As a family man, Peart owed an enormous amount to his wife, Peggy. He died on 14 March 2019. He was one of the last real professors of medicine – a scientist, a teacher and always a clinician. Those who followed and were fortunate to have worked with him remember the brilliant mind, the charisma, the sense of humour and, perhaps, the bow tie and the red socks.

Written by Peter Sever (Imperial College London).

# Obituary: Paul M Vanhoutte 1940 – 2019

Paul M Vanhoutte

"Publishing extensively in both *The Journal of Physiology* and the *American Journal of Physiology*, his scientific output was prodigious: he co-authored or edited 36 books, published 669 original research papers, and 574 editorials and reviews"

Paul M Vanhoutte died in Paris, France, on 23 August 2019 after a fall. He will be remembered as a leading figure in cardiovascular physiology and pharmacology and as a great friend and mentor by those who were lucky enough to work with him.

Born and trained as an MD in Belgium, Paul received his postdoctoral training in the Department of Physiology at the Mayo Clinic in Rochester with JT Shepherd, who surely infected him with the physiology bug. Paul's subsequent career spanned academia, industry and three continents. He held professorial positions at the University of Antwerp, The Mayo Clinic, and Baylor College of Medicine. In 1992 he moved into industry as Vice President of R&D at the Institut de Recherches Internationales Servier, in France. However, in 2003, and until his death (he never retired), he returned to academia, becoming Distinguished Visiting Professor and the Director and Founder of the Biopharmaceutical Development Centre at the University of Hong Kong.

His early research evolved from a study of the control of the veins to understand why acetylcholine is a vasodilator. This led him to research the control of sympathetic neuro-effector junctions and of the interaction of vasodilator and vasoconstrictor substances with the vascular endothelium. His major scientific contribution was the analysis of the importance of endothelial cells for the control of vascular smooth muscle in health and disease. Publishing extensively in both *The Journal of Physiology* and the *American Journal of Physiology*, his scientific output was prodigious: he co-authored or edited 36 books, published 669 original research papers, and 574 editorials and reviews. On the editorial boards of numerous physiology and pharmacology journals, he was particularly exercised to ensure the highest quality of scientific publication, and became Editor-in-Chief of the *Journal of Cardiovascular Pharmacology* and an Associate Editor of the *American Journal of Physiology* (Heart and Circulatory Physiology).

Paul was a polymath but certainly regarded physiology as one of his prime disciplines. Physiology underlay his interests in pharmacology and medicine. At each International Congress of IUPS for many decades Paul was involved with the organisation of a series of satellite meetings called "Mechanisms of Vasodilatation". It was at one such meeting that, at Paul's invitation, Robert Furchgott gave one of his first talks on his new ideas about an endothelium-derived relaxant factor, the seminal work that led to a huge explosion of work on the physiological roles of the endothelium, and ultimately to Furchgott's Nobel Prize in 1998. It is hard to underestimate Paul's contribution to this field. Named lectures have been established in his honour and he received honorary doctorates from nine universities. A member of many learned societies, he was also one of the few who have been awarded honorary membership of both The Physiological Society (in 2009) and The British Pharmacological Society.

Those of us who had the privilege to work with him will always remember his charismatic scientific leadership and guidance. He had unbounded energy and enthusiasm for science, for people and for life. He travelled prodigiously, meeting all the leading cardiovascular researchers. We will not forget the metal briefcase (or was it two?) containing slides that he carried around on the off-chance that he would be expected to concoct a talk. On a visit to Scotland he actually gave two entirely different talks for different audiences, all made up in about half an hour, once he knew who the audiences were.

Paul inspired a genuine warm loyalty from all who ever spent time with him. At every major scientific conference, there would be an impromptu Paul Vanhoutte dinner attended by all the ex-trainees attending the conference. If there was a conflict with any other event, it was the other event that would be missed. In particular a surprise 60th birthday gathering was held for him in Paris where over 100 former mentees from around the world paid their way to celebrate the day.

Paul was generous and astute with advice, great fun to work with and also to relax with after work. He enjoyed good company, good food, good wine and good jokes (and the occasional cigar). He had many memorable sayings such as "I feel a paper coming on" and "There are three kinds of people, those who make things happen, those who watch what happens and those who wondered what happened". He was in the first category and made good things happen for the young scientists he trained during his career and for his co-workers.

Paul Vanhoutte leaves a wife Jacqueline, four children and seven grandchildren. All who knew him will remember his scientific insight and influence, his "art-de-vivre", the seemingly impossible travel schedules, his quick wit and his infectious laugh.

Written by Michael Collis (Retired) and Ian McGrath (University of Glasgow and University of Sydney).

**Further reading**

Boulanger *et al.* (2019).Tribute to Paul M. Vanhoutte, MD, PhD (1940 – 2019). *Arteriosclerosis, Thrombosis, and Vascular Biology* **39**, 2445 – 2447. DOI: 10.1161/ATVBAHA.119.313461

See also the "Paul M. Vanhoutte – Commemorative Issue" published by *The Journal of Physiology* in November 2019. DOI: 10.1113/JP279124

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