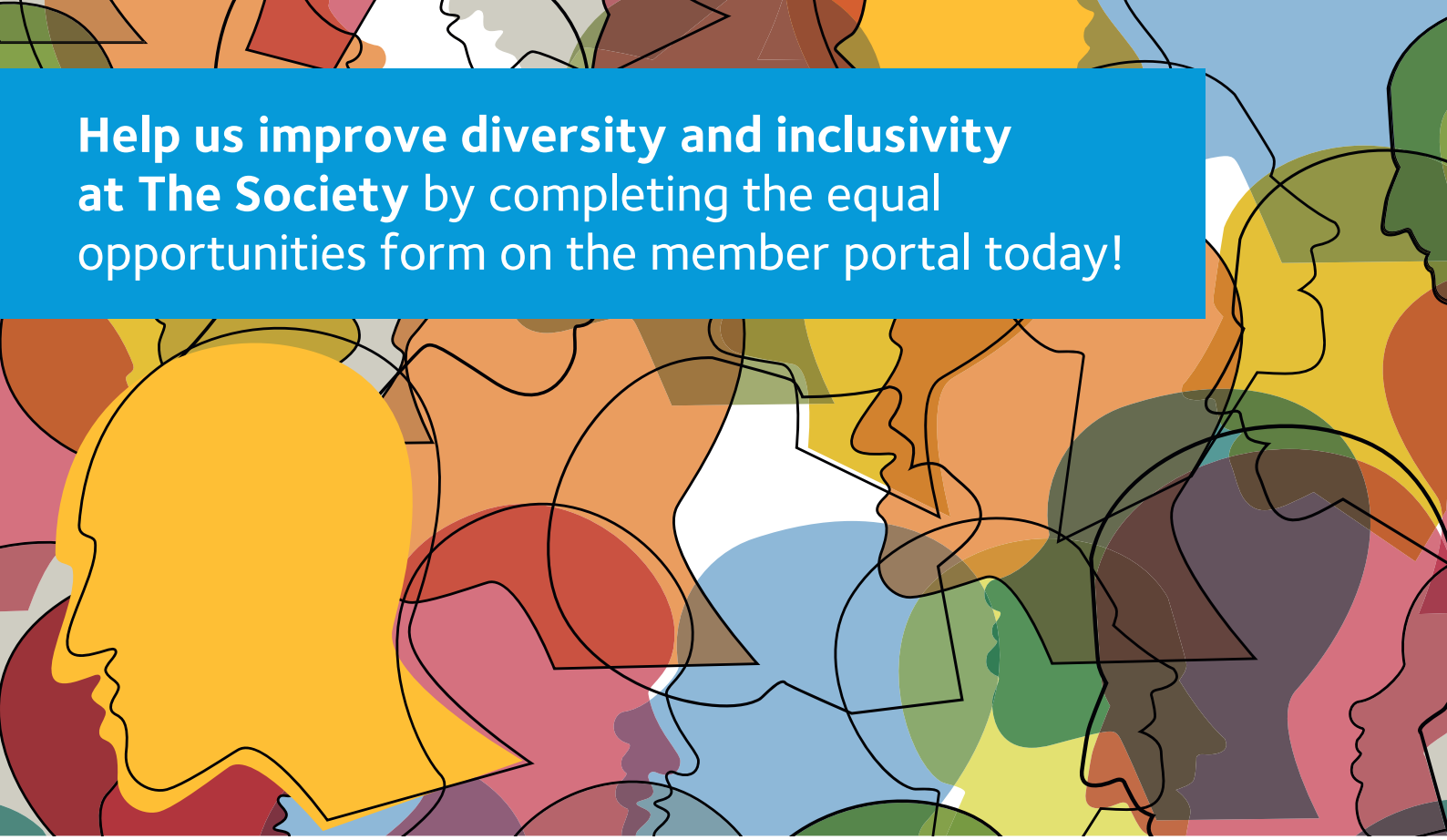
Issue 113 / Winter 2018

PN Physiology News

Chronobiology and Sleep

Special issue

The Physiological Society



Help us improve diversity and inclusivity at The Society by completing the equal opportunities form on the member portal today!

The Physiological Society

For more information about The Society's Diversity and Inclusion work go to: **www.physoc.org/diversity**

Physiology News

We welcome feedback on our membership magazine, or letters and suggestions for articles for publication, including book reviews, from our Members.
Please email Julia Turan at **magazine@physoc.org**.

Physiology News is one of the benefits of membership, along with reduced registration rates for our high-profile events, free online access to our leading journals, *The Journal of Physiology*, *Experimental Physiology* and *Physiological Reports*, and travel grants to attend scientific meetings. Membership offers you access to the largest network of physiologists in Europe.

Join now to support your career in physiology:
Visit **www.physoc.org/membership** or call **0207 269 5721**.

Membership Fees for 2018/2019	FEES
Fellow	£120
Member	£90
Retired Member	–
Affiliate	£40
Associate	£30
Undergraduate	–

Opinions expressed in articles and letters submitted by, or commissioned from, Members or outside bodies are not necessarily those of The Physiological Society. *Physiology News* is a member magazine and therefore is not subject to peer review and authors are advised to not include unpublished hard scientific data.

magazine@physoc.org

www.physoc.org

@ThePhySoc
/physoc
/company/The-Physiological-Society
/physoctv

Designed, produced and printed by Lavenham Press Ltd.

Welcome to the Winter 2018 edition of *Physiology News*

Introduction

News & Views

Events

Journal Insights

Features

Membership

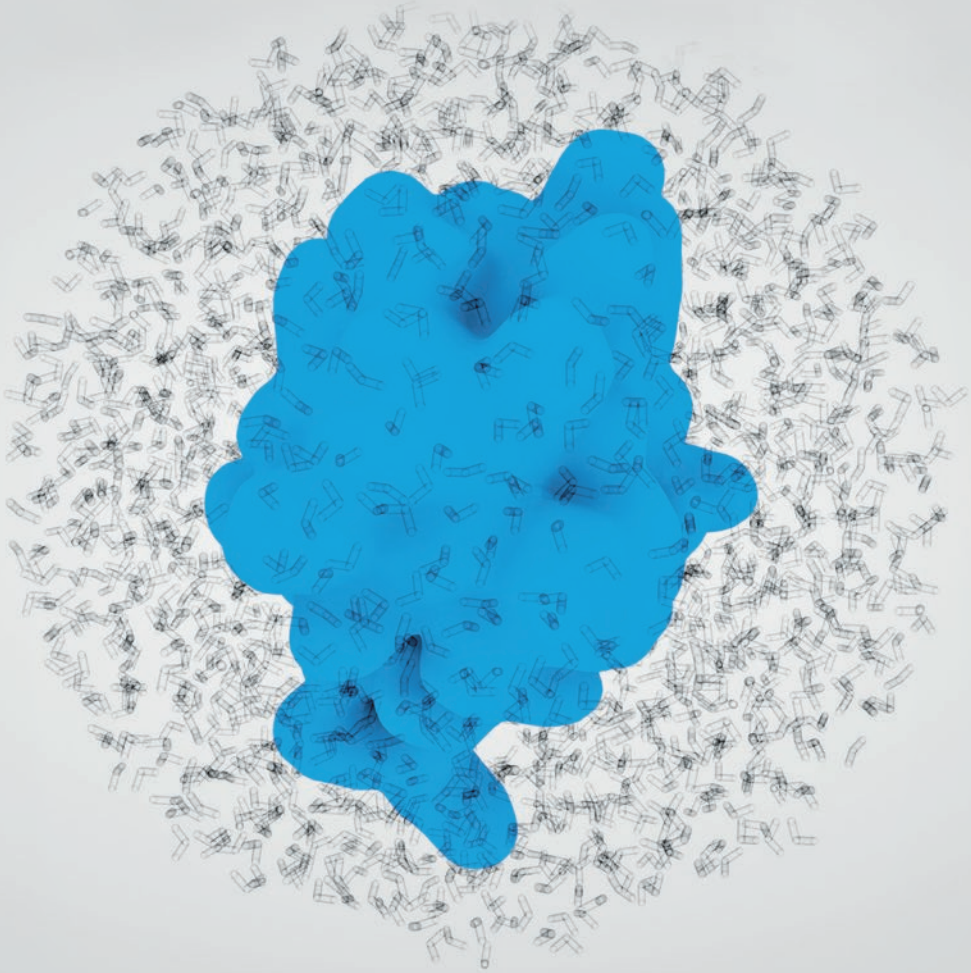
Cover image: We acknowledge the use of imagery from the NASA Worldview application (**https://worldview.earthdata.nasa.gov/**) operated by the NASA/Goddard Space Flight Center Earth Science Data and Information System (ESDIS) project.

#LifeSci19

Life Sciences 2019:

A key meeting about post-translational modifications (PTMs) in biological processes

The Physiological Society, **British Pharmacological Society** and **Biochemical Society** are joining forces to bring you the latest research and discuss important challenges.



Life Sciences 2019:
Post-Translational Modifications and Cell Signalling

17-18 March 2019
East Midlands Conference Centre, Nottingham, UK

Submit your abstract by 21 January 2019: **bit.ly/ls19abstract**

BIOCHEMICAL SOCIETY

BRITISH PHARMACOLOGICAL SOCIETY

The Physiological Society

A year of chronobiological discourse in science and society

Philip Lewis

University Hospital of Cologne, Germany

2018 has become a year for light, time and chronobiological discourse in science and society. Thus, we considered it timely to publish this themed issue to educate and inspire chronobiological thinking amongst physiologists at all career stages.

In August, citizen surveys and a European vote to abolish the biannual clock time change indicated a preference for the advanced summer clock all year round. Consequences include a lack of early morning daylight experienced in winter time, especially on the edge of time-zones and in more northern latitudes where the sun would not rise until well after 9 am. As morning daylight is a key time cue for the body's circadian system, which temporally organises physiology, children and adults getting up and going to school or work in darkness may suffer continuous circadian misalignment throughout the winter period. In the short-term, we may expect increased traffic and workplace accidents, and poorer performance in schools due to debilitating effects on cognitive and physical performance, and sleep impairment. In the long-term, significant debilitating effects on metabolic and psychiatric health would be expected given the important co-governing roles of the circadian system on metabolic and psychiatric physiology.

Also in August, the International Agency for Research on Cancer (IARC) called for data relevant to the proposed carcinogenicity of shift-work that causes circadian disruption. The current Group 2a ("probable") classification is to be reviewed in Lyon in June 2019. Importantly, significant portions of the population (around 21% of the EU workforce) are engaged in shift work which can be disruptive to chronobiology and sleep. "Living for the weekend," whereby people tend to stay up later and sleep in later than on work days, can be equally disruptive to circadian systems. Moreover, there is increasing 24–hour access to various amenities which, along with light at night from light-emitting devices such as smartphones and tablets, can also throw biological rhythms out of sync with each other and contribute to what is already considered a sleep deficiency pandemic.

In October, the Chinese government announced a proposal to launch satellites in 2020 that will provide a continuous full-moon-like light glow over the Chengdu region by reflecting sunlight similar to the moon. Just as daylight is important for entraining a strong and stable circadian rhythm, so is darkness. A change over from light to dark also provides the body with a sense of time, such as indicating the appropriate sleep period for humans or wake period for nocturnal animals. The impact of continuous full-moon-like light at night on circadian and lunar-light rhythms of humans, other animals, and plants is unprecedented.

From a physiological perspective, we have chronobiological co-governance of large portions of the genome and biochemical processes in every cell as well as chronobiological communication within and between tissues and organs. All of this provides a temporal organisation to physiology in response to ubiquitous environmental time cues such as the daily light-dark cycle and meal times. Such extensive co-governance of physiology means the contribution of disrupting circadian physiology to the global burden of disease could be grossly under-appreciated. Metabolic and mood disorders, and cancer may just be the tip of the iceberg.

But there may be light at the end of the tunnel.

Such an extensive system of co-governance also means that appropriate timing of medical interventions could significantly impact efficacies or decrease side-effects. Understanding how perturbation to, or reinforcement of, circadian rhythm could impact physiology could have significant health-care and economic impact. Importantly, chronobiology is ubiquitously applicable to physiology sub-disciplines. Thus, physiology can have a massive role to play in the chronobiology field going forward. Furthermore, chronobiological and sleep concepts are readily understood by a non-scientific audience. For instance, the association of sleep–wake cycles with day and night is conspicuously recognisable: folk wisdom will tell us to avoid eating large meals late at night, and exacerbations of diseases are often associated with time of day, even to patients of the common cold. As such, advances in chronobiology may be quickly and easily translated to benefit individuals and populations.

The content herein – including chronobiology history, education, prevalent issues, contemporary studies, philosophical questions, collaboration, and translations of research – will not disappoint. Given the hot topic nature of this field, near universal applicability for physiological research with a clock in every cell, and that every individual in the world is exposed to light, dark, and other circadian time cues, it is both a pleasure and a privilege to be Guest Editor for this Chronobiology and Sleep Special Issue of *Physiology News*, and to fittingly end the year in line with The Society's Theme for 2018.

Heightening focus on chronobiology now could be *the stitch in time that saves nine*!

On the topic of mysteries of the action potential

For science to thrive, we must always be willing embrace and facilitate substantive debate. Even the long established and most well-regarded of our theories must be open to challenge and withstand constant experimental scrutiny. "Mysteries of the action potential" in *Physiology News* 111 stoked such a debate, and we received several letters to the editor which we have published together with responses from the authors.

Action potential conduction is not a mystery

James A Fraser
Department of Physiology, Development and Neuroscience, University of Cambridge, UK

Ron R Horgan
Department of Applied Mathematics and Theoretical Physics, University of Cambridge, UK

The article "mysteries of the action potential" (*Physiology News* 111, p.38-41) suggests that action potential propagation cannot be understood by cable theory. We are pleased to reassure readers that it can be; instead, the problem appears to be that the article's authors do not understand cable theory.

At the heart of Johnson and Winlow's article is a complete misunderstanding of how electrical conduction works. Thus, the authors repeatedly claim that the mechanism of action potential propagation as described by cable theory is either impossible or too slow to account for nerve conduction. They state, for example, that "the physical properties of Na^+ ions cannot allow flow of charge from one ion channel to the next in the time available" and "a conservative simple Speed-Time calculation suggests that the maximum speed Na^+ ions can travel between channels is less than a thousandth of what is necessary for propagation." These statements are simply wrong, and it is surprising that they have been published.

Na^+ ions do not quickly diffuse from one ion channel to the next, but nor do they need to. Instead, as Na^+ ions enter the axon they cause an increase in local net positive charge density. This generates an electric field (a voltage gradient) that drives a current along the axon. Johnson and Winlow's statements above appear to refer to the drift velocity of the injected Na^+ ions; to correctly understand how one ion channel might trigger the next, they must instead consider the electrical current that results from this Na^+ entry. The current is carried by all mobile ions in the electrolyte and, just as in any conductor, the nature of the charge carrier is immaterial except in how it determines the electrical conductivity. This conductivity may be measured or calculated easily. As it happens, K^+ is the most prevalent intracellular ion and hence the principle charge carrier. The K^+ concentration is many orders of magnitude larger than that of the newly injected Na^+ ions, perhaps explaining why Johnson and Winlow's calculations based on Na^+ mobility are incorrect by a similar margin.

Cable theory then derives from similar statements of very basic physics that apply to transmission lines in general: put simply, ionic charges produce an electric field; ionic solutions are electrical conductors; conductors separated by thin insulators have a capacitance. The axon is, in this respect, a high loss coaxial cable. The theory that describes such cables has been known for well over 100 years. Its application to nerve conduction can be derived fairly straightforwardly (e.g. Rall, 2011). Indeed, more recent work has demonstrated that extensions of cable theory reproduce and predict excitability and conduction velocity even in the more complex membrane architecture of skeletal muscle (Pedersen *et al.*, 2011; Fraser *et al.*, 2011).

Thus, the proposed soliton model is unnecessary. It is not described in sufficient detail to be fully understood or analysed. However, there are some obvious flaws in the theory. What roles do K^+ channels play? Would these sound-like waves not decay in amplitude where cable diameters increased, such as from a nerve dendrite to its soma? Why do action potentials travelling in opposite directions cease at the point of collision, when sound waves would pass through one another?

In conclusion, conduction in biological tissues is well described by cable theory. There is certainly more to learn about excitable tissues under physiological and pathological conditions. However, those studying these systems should seek to understand, rather than reinvent, the relationships between voltage, conductance, capacitance and current.

References

Fraser JA, Huang CL-H, Pedersen TH (2011). Relationships between resting conductances, excitability, and t-system ionic homeostasis in skeletal muscle. *Journal of General Physiology* **138**, 95–116.

Pedersen TH, Huang CL-H, Fraser JA (2011). An analysis of the relationships between subthreshold electrical properties and excitability in skeletal muscle. *Journal of General Physiology* **138**, 73–93.

Rall W (2011). Core Conductor Theory and Cable Properties of Neurons. In *Comprehensive Physiology*. Hoboken, NJ, USA: John Wiley & Sons, Inc.

Classical experiments had already "demystified" the action potential

David Miller
School of Life Sciences, University of Glasgow, UK; History and Archives Committee, The Physiological Society

The electrical nature of the action potential is nothing like so "mysterious" as Johnson and Winlow suggest (*PN* 111, p.38-41). James Fraser and Ron Horgan have addressed one aspect, explaining the true nature of electrotonic conduction in nerve or muscle fibres. Here, I detail further physiological phenomena that contradict

the "soliton" concept of action potential (AP) propagation.

The authors perhaps overlooked long-known observations such as the macroscopically detectable intra- and extra-cellular local circuit currents that spread ahead of the AP. Thus, reducing extracellular resistance (ro) increases the AP propagation speed, just as cable theory predicts. Hodgkin (1939) showed this by placing a nerve prep (crab or squid single axons) on platinum plates to reduce ro, whereas increasing ro by oil bath immersion or air exposure slowed the AP. None of this is explicable with the mechanical "soliton" that would proceed unaffected by these "remote" extracellular modifications having only electrical "relevance".

A "soliton" account of saltatory conduction in myelinated fibres (see Johnson & Winlow, 2018) is also unpersuasive. Their model offers no obvious role for axoplasmic resistance and thus in explaining how a greater diameter increases conduction velocity (CV) in myelinated and unmyelinated fibres. Cable Theory accurately predicts the linear relationship of diameter to CV in myelinated axons as against the square-law relationship for unmyelinated fibres. Such modelling predicts the evolutionarily optimised ratio of 0.6 of conducting "core" to overall insulating "sleeve" diameter, as observed in peripheral myelinated axons. And last, myelination theoretically becomes disadvantageous in the smallest axons (Rushton, 1951, Fig. 5): indeed, below that predicted size, myelination is not observed. Rushton (1951) detailed all this: it cannot be accounted for by the "soliton".

The 'soliton' model also fails to account for liminal length considerations. Again, Cable Theory reveals why a minimum area of membrane must be activated to sustain propagation. Sufficient current – thus a cylindrical length of axon membrane with its complement of activated channels - is required to discharge the capacitance of the neighbouring region sufficiently to bring it above threshold: the liminal length for an excitable cell.

A final twist is that the authors perhaps overlooked one of the very first observations relevant to our understanding of the intrinsically electrical nature of activity in nerve and muscle. This is the phenomenon of "ephaptic" excitation first described by Galvani (e.g. 1794), as used to be demonstrated by some of us to junior Physiology and Medicine students. I refer to the experiment where extrinsic current flow around an activated frog gastrocnemius muscle, triggered via its sciatic nerve, is sufficient to excite a second sciatic-gastrocnemius preparation: the second nerve is merely draped over the first muscle. The first sciatic can be activated by a squeeze with forceps: the resulting injury potential accounts for the activation in that nerve, thence the first muscle and the second sciatic and gastrocnemius activate in turn. None of this need involve batteries and electrodes. Galvani's observation contributed to contemporary consideration of whether "animal electricity" was intrinsically different from that produced by physico-chemical means ("Voltaic piles" etc.). Any "mechanical" soliton propagation/excitation between the anatomically separate first muscle and second nerve can obviously be discounted.

None of these long-established phenomena can plausibly be accounted for in the "soliton" scheme. By contrast, Cable Theory provides a coherent, testable and quantifiable account of all of them.

I suggest that any mechanical disturbance of the transmembrane channel proteins that accompanies the AP is itself an epiphenomenon. One expects the deformation of activated channels that allows ions to pass through would have mechanical sequelae. Channel proteins sit in a voltage field of 100 mV expressed across 10 nm, or 100 kV/cm: a huge field strength. Deformation upon voltage change is very understandable. But expecting such nanometre-scale perturbations to propagate over a millimetre or more of internode in larger myelinated axons surely stretches credulity. (The internodal length in larger axons is some 100,000 times the axonal membrane thickness, or more). That a mechanical wave generated at nm dimensions can propagate over such distances would require a "stiffness" of the lipid bilayer – itself a dynamic, fluid, physical phase - that cannot be credible.

References

Galvani L (1794). *Dell'uso e dell'attività dell'arco conduttore nelle contrazioni dei musoli.* San Tommaso d'Aquino, Bologna.

Hodgkin AL (1939). The relation between conduction velocity and the electrical resistance outside a nerve fibre. *Journal of Physiology* **94**, 560-570.

Johnson AS, Winlow W (2018). The soliton and the action potential – primary elements underlying sentience. *Frontiers in Physiology* **9**, 779. DOI: 10.3389/fphys.2018.00779.

Rushton WAH (1951). A theory of the effects of fibre size in medullated nerve. *Journal of Physiology* **115**, 101-122.

Responses from the feature authors

Andrew Johnson
Neuroscience & Physiology Consultants (NPC)
Newton, France

Bill Winlow
University of Naples Federico II, Italy;
University of Liverpool, UK & NPC Newton, UK

Our general response to the letters above is as follows. Point-by-point specific responses to each letter are given below.

At issue is not whether the action potential can be understood by Cable Theory but is it correct to do so. A correlation with Cable Theory is not evidence, unless the underlying molecular activity matches the model and it does not.

The APPulse is a soliton pulse synchronised with the action potential; it will therefore have many of the same attributes, because any model of the nerve impulse must account for the activity produced at the molecular level of the membrane. In either the APPulse or Cable Theory the ion channel properties are identical and opening of the channels takes place in both models.

However, the Hodgkin and Huxley (HH) model does not include a modern understanding of either the membrane or the ion channels because this knowledge was unknown at that time and our article presented evidence unavailable to them. In particular, we now have detailed knowledge of the ion channel structure and function, as well as channel reconfigurations and subsequent shape changes and the mechanical changes that can cause them to open. In the HH model, the absence of closely aligned ion channels gives no coherent mechanism for them to be sequentially activated or to explain the refractory period of single ion channels. In contrast, in the APPulse a detailed description is given of the electrostatic and geometric changes that match precisely the entropy changes, the morphology changes and the "electrical" changes.

What is not explained by HH is the destiny of the entropy derived from the opening of the ion gates - if they are attached to the membrane then the membrane will move and it is logical to conclude that this entropy is transferred to the ever-present soliton accompanying the action potential. In Cable Theory and during the APPulse the membrane would inevitably move. Only the APPulse explains the entropy change. Furthermore, the mathematics and properties of solitons are now much

better understood. We now know that a soliton always accompanies an action potential and solitons have recently been visualised using interferometric imaging (Ling *et al.,* 2018).

Thus, there is now overwhelming evidence that a soliton travels with the action potential. Movement of ion channels will therefore cause movement in the membrane in both models. We know the soliton is synchronised to the action potential, arriving just before the ion channel opens. The major difference between the APPulse and Cable Theory is the mechanism of activation of the ion channels – mechanical or electrical. Given that there will always be a soliton present it is therefore logical that this is the mechanism for activation.

The APPulse satisfies the requirements of entropy and transmission according to the knowledge we now possess of the mechanisms available at the membrane (for more detail, see Johnson and Winlow, 2018). Because the APPulse is based upon the action potential, it contains many of its elements with the addition of the synchronised soliton and its activation of ion channels by mechanical force.

In scientific research there are often conflicts between groups of scientists supporting opposing theories, but quite often the opposing theories unify and a composite hypothesis emerges later. For example, in the 1950s it had just become widely accepted that synaptic transmission was by chemical rather than electrical means when electrical transmission was conclusively demonstrated in the crayfish by Furshpan and Potter (1957; 1959). We have therefore used current data to illuminate the older and well-verified HH model and have combined those ideas into the concept of the APPulse – a useful working model – although others may suggest that no such compromise is possible and that nerve cells communicate with mechanical pulses, not electrical pulses (see Fox, 2018 for background).

Responses to James A Fraser & Ron R Horgan

Paragraph 1: No, we do not agree that Cable Theory can provide the explanation of propagation and we think there is still some mystery to the underlying mechanism, best explained with soliton theory.

Paragraphs 2 & 3: We dispute that inter-ionic charge effects at the site of ion release would make any difference. Local charge activity could not affect the ion channels. When Cable Theory was proposed inter-channel distances and activity were not known as they now are. Charged Na^+ ions exiting from an ion gate produce a local field. This field will affect nearby ions (any ions) but it is not directional along the axon but into the cytoplasm and any resultant field would dissipate quickly because of entropy lost. For charge to propagate along a membrane, anions would have to move correspondingly and directionally without interaction of cations as in near-adiabatic processes. The only other forces are diffusional.

Paragraph 4: This is not an argument, as once again both models would almost certainly apply. In cardiac muscle one of the more important aspects is to consider how the elements that compose the excitation-contraction coupling synchronise. In the APPulse all elements are synchronised by the mechanical activation of the ion channels to the contraction of the muscle. In accepting Cable Theory the basic mechanical action of the heart muscle to be synchronised to the cardiac action potential is overlooked.

Paragraph 5: There is substantial evidence in the biophysical literature to describe solitons. In answer to the question "Why do action potentials travelling in opposite directions cease at the point of collision, when sound waves would pass through one another?", solitons lose entropy to their surroundings. Collision of two APPulses results in areas around the collision in both directions becoming refractory and the entropy of the soliton will decay without entropy recharge from the ion channels. Cancellation of the APPulse by another is not therefore a property of the soliton itself.

Hodgkin and Huxley only suggested Cable Theory as a model not as the mechanism it has become in accepted orthodoxy. We now know the most likely configurations of the ion channels and the selector site for activation of Na^+ channels. The horizontally directed expansion of the activated channels is the only mechanism that can add entropy to the always present soliton. There is no evidence indicating that charge can spread from one ion channel to the next in the timing required. Cable Theory does not explain the soliton nor the entropy changes but the APPulse does.

Responses to David Miller

Paragraphs 1 & 2: Ion channels open on membrane potential change and this is not disputed. There would be no difference between the two models in this case.

Paragraph 3: Rushton himself describes the relationship as a coincidence and in any case the rules would apply similarly to a pulse.

Paragraph 4: This would apply equally to a soliton flow along a cylinder. The activation of a pulse in a cylinder requires sufficient entropy – the same entropy provided by the ion gates.

Paragraph 5: As stated, ion channels are opened by both change in potential and mechanics. This is exactly the same in both HH and the APPulse. Any stimulation would cause contraction in either model.

Paragraph 6: All these long-established phenomena can be accounted for by the APPulse as explained above.

Paragraph 7: The soliton is a pulse travelling along the surface of a cylinder in which entropy is directed only in the direction of propagation. This is an entropy-closed system due to the surface linking of the impulse around the circumference during propagation. Loss of entropy in such a situation is minimal. In addition our knowledge of membranes indicates that a soliton can propagate very long distances. Contrast this with the situation in Cable Theory where charge is proposed to spread this same distance – no local currents could achieve this. For propagation of the impulse between ion channels the soliton is the best candidate.

References

Fox D (2018). The brain, reimagined. *Scientific American* **318**(4), 60-67.

Furshpan EJ, Potter DD (1957). Mechanism of nerve-impulse transmission at a crayfish synapse. *Nature* **180**, 342-343.

Furshpan EJ, Potter DD (1959). Transmission at the giant motor synapses of the crayfish. *Journal of Physiology* **145**(2), 289-325.

Johnson AS, Winlow W (2018). The soliton and the action potential – primary elements underlying sentience. *Frontiers in Physiology* **9**, 779. DOI: 10.3389/fphys.2018.00779.

Ling T *et al.* (2018). Full-field interferometric imaging of propagating action potentials. *arXiv*:1807.03269 [physics.bio-ph].

Welcoming our new President, Bridget Lumb

Bridget Lumb

President, The Physiological Society

Carrying on the tradition initiated by my predecessor David Eisner, I intend to publish a "President's View" article in each issue of *Physiology News* to keep you abreast of my take on things.

For those of you who don't know me, I'm a Professor of Neuroscience at the University of Bristol and my research interests focus on central nervous system mechanisms of pain and fear. I have a longstanding and affectionate relationship with The Physiological Society; I joined The Society in 1990 and have served on several of its committees (including Education, and Animal Legislation and Welfare), acted as Deputy Editor-in-Chief of *Experimental Physiology* and was Meetings Secretary from 2002 to 2006. I am now honoured to become President of The Society and am very much looking forward to the next two years in this role.

I'm extremely fortunate to take on the presidency at this particular time. In addition to ongoing activities aligned to our charitable objectives (including Education, Policy, Meetings and Publications), Council and Society staff, led by the Chief Executive Officer (Dariel Burdass), have spent much time over the last two years "putting The Society's house in order" and, at the same time, planning for the future.

Putting our house in order was in some respects quite literally that. As part of repurposing the internal layout of our headquarters, Hodgkin Huxley House (HHH) to optimise the facilities for our staff and, at the same time, the financial return from our tenants, we discovered that significant remedial work on the external structure of the building was needed. These works are now complete and we have tenants occupying three, rather than two, floors. The building is in good condition and a maintenance programme is in place going forward. The other important work to put our house in order was the development of The Society's strategic plan with a vision of ensuring that "physiology flourishes" and an overhaul of our governance structure. The strategic plan is now complete (and is available on our website at **bit.ly/2KdkIck**), whereas the governance review will be presented, discussed and hopefully agreed at the December meeting of Council. A critical, ongoing project is the launch of our new website with appeal to a wider audience and greater accessibility.

We owe thanks to our very professional team at HHH who, under the capable leadership of Dariel Burdass, together with my predecessor David Eisner and the Trustees, has achieved a great deal in the last two years. Their efforts and vision have meant that I take on the presidency at a time when The Society is in a solid position to ensure that physiology flourishes. The next two years will not be without challenges, however. One of my priorities is to ensure that we plan for the financial future in a world of open access publishing. As part of this, Council will be working with Finance Committee to review The Society's Reserves Policy to ensure we have the appropriate resilience against, for example, the demands of a new project or drops in income. Another priority will be to work with Trustees and staff to develop membership strategies, following on from Member Insight Project feedback, by reviewing member benefits and exploring how we might enrol Members from a wider spectrum of backgrounds. Lastly, we will work to ensure that our scientific meetings continue to provide world-leading platforms for the dissemination of our science and education programmes to a wide audience, including the public.

"We owe thanks to our very professional team at HHH who, under the capable leadership of Dariel Burdass, together with my predecessor David Eisner and the Trustees, has achieved a great deal in the last two years"

In sum, I'm very much looking forward to working with the membership, Council and the staff at HHH at what is a very exciting time for The Society.

Time for a medical revolution

Gabriele Sulli

Salk Institute for Biological Studies, California, USA

The evolutionarily conserved biological clocks in organisms provide temporal organisation for the performance of specific physiological functions. In humans for example, blood pressure, body temperature, blood concentrations of melatonin, insulin, corticosteroids, and adrenaline, and many other crucial physiological nodes display nearly 24-hour (=circadian) cyclic rhythms.

But what happens when the clock is perturbed or broken? In recent years, accumulating evidence suggests that disruption of circadian rhythms precedes the advent of several neurodegenerative diseases and has been causally connected with development of obesity, diabetes, cardiovascular diseases, and even the aging process (Sulli *et al.,* 2018). In 2007, the WHO agency IARC (International Agency for Research on Cancer) even included circadian disruption caused by shift work in the list of agents probably carcinogenic to humans (IARC Working Group, 2010).

The circadian clock is a powerful regulatory machine co-governing a complex web of physiological processes. We know that alterations of the clock can have devastating consequences for the maintenance of homeostasis. Thus, we are reaching a crucial time in biology and medicine where we will need to start addressing some fundamental chronobiology questions: Can time be a crucial parameter to consider in the quest of personalised medicine? Can we exploit the clock to improve patient treatment and derive new therapeutic strategies? Physiological research will inevitably have a major role to play in providing answers to these questions.

Already in the 1970s and 1980s, pioneering studies were underway to assess whether the timing of treatments could be an important parameter in determining outcomes via mechanisms such as reducing toxicity in cancer chemotherapy (Haus *et al.,* 1972; Halberg *et al.,* 2006; Hrushesky, 1985). More specifically, studies in advanced ovarian cancer patients addressed whether a carefully scheduled timing of cyclophosphamide or a combination of adriamycin and cisplatin could improve adverse drug reactions (Halberg *et al.,* 2006; Hrushesky, 1985). Patients treated with cyclophosphamide at 4.00 am and adriamycin in the morning and cisplatin in the evening experienced fewer toxic effects. Thus began cancer chronotherapy (Halberg *et al.,* 2006; Hrushesky, 1985).

Chronotherapy aims to reduce adverse drug reactions and optimise drug efficacy by timing drug administration in accordance with the body's circadian rhythms. The principle is very simple and derives from practical observations showing that patients treated at different times but with the same drug experience differential levels of toxicity or improvements in drug efficacy. With regard to the latter, if the expression of a drug target fluctuates periodically, then said drug will be more efficient if administered when the target is expressed at its highest level.

Further cancer chronotherapy trials have been conducted with different therapeutic agents including cisplatin, oxaliplatin, radiotherapy, folinic acid and fluorouracil in patients with breast cancer, non-small cell lung cancer, head and neck cancer, metastatic colorectal cancer, metastatic bladder cancer, metastatic endometrial cancer, metastatic renal cell carcinoma, cervical cancer, and prostate cancer. While studies with small cohorts have been promising, larger trials have unfortunately curbed in enthusiasm for this approach. Whilst the principle is simple and intuitive, in 2016 only 0.16% of clinical trials were taking the timing of the drug administration into account (Selfridge *et al.,* 2016). One reason for the inconsistency of large trials is that each individual enrolled in a trial will have his/her own rhythms, i.e. the timing of drug target peak expression

More recently, several studies have shown that evening administration of statins (especially those with short half-life) is associated with better outcomes because peak activity of HMG-CoA reductase (statin's target) occurs in the liver at night. Other disorders where a chronotherapeutic approach could provide benefits, beyond cancer and hyperlipidaemia, include asthma, allergic rhinitis, arthritis, peptic ulcers and hypertension, inflammatory diseases, and type 2 diabetes (Sulli *et al.,* 2018).

may differ between individuals. Indeed, such timing may differ on a day-to-day basis in a given individual. A late dinner or a sleepless night can have a strong impact on the circadian clock and misalign the patient rhythms with the pre-fixed timing of the drug administration.

Is chronotherapy destined to remain a beautiful concept with no practical actuation in real life? Recent innovations suggest otherwise. Technological advancements that may aid personalised chronotherapy

include wearable devices to assess rest/activity cycles and light exposure and blood tests to easily check the status of circadian rhythms (Wittenbrink *et al.*, 2018). Moreover, progress is being made on tools to automatically release drugs in time alignment with biological rhythms and will allow performance of better chronotherapy trials. Personalised chronotherapy could be the new way forward. As drug timing affects efficacy, re-evaluation of many drug candidates that have been put aside by pharma companies may be warranted. Chronotherapy, therefore, holds a lot of promise.

Beyond chronotherapy, strengthening the link between the circadian clock and medicine may lead to additional innovations. Indeed, although still in a primordial phase of development, drugs targeting circadian clock regulators may provide new therapeutic strategies against various diseases. Recently, for instance, observations showing that pharmacological modulation of REV-ERBα and REV-ERBβ (two crucial circadian regulators) is selectively lethal in cancer cells in culture and in glioblastoma animal models and it seems to have a wide therapeutic window with limited toxic effects (Sulli *et al.*, 2018). Such observations shedding light on a new therapeutic paradigm could put the circadian clock machinery at the centre of the next pharmacological revolution. In the future, many disorders may benefit from the development of drugs targeting circadian clocks such as metabolic and mood disorders, jet lag, and others. It's time for a new era of medicine.

References

Halberg F, Prem K, Halberg F (2006). Cancer chronomics I. Origins of timed cancer treatment: Early marker rhythm-guided individualized chronochemotherapy. *Journal of Experimental Therapeutics and Oncology* **6**, 55-61.

Haus E, Halberg F, Pauly JE *et al.* (1972). Increased tolerance of leukemic mice to arabinosyl cytosine with schedule adjusted to circadian system. *Science* **177**(4043), 80-82.

Hrushesky WJ (1985). Circadian timing of cancer chemotherapy. *Science* **228**(4695), 73-75.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2010). Painting, firefighting, and shiftwork. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* **98**, 9-764.

Selfridge JM, Gotoh T, Schiffhauer S *et al.* (2016). Chronotherapy: Intuitive, sound, founded... but not broadly applied. *Drugs.* **76**(16), 1507-1521.

Sulli G, Manoogian ENC, Taub PR *et al.* (2018). Training the circadian clock, clocking the drugs, and drugging the clock to prevent, manage, and treat chronic diseases. *Trends in Pharmacological Sciences* **39**(9), 812-827.

Sulli G, Rommel A, Wang X *et al.* (2018). Pharmacological activation of REV-ERBs is lethal in cancer and oncogene-induced senescence. *Nature* **553**, 351-355.

Wittenbrink N, Ananthasubramaniam B, Münch M *et al.* (2018). High-accuracy determination of internal circadian time from a single blood sample. *Journal of Clinical Investigation* **128**(9), 3826-3839.

Congratulations to the R Jean Banister and GL Brown Prize Lecture awardees!

Congratulations to Nathalie Rochefort, awardee of the R Jean Banister Prize Lecture, and Andrew Parker, awardee of the GL Brown Prize Lecture. Rochefort's lecture, entitled "Decoding the visual cortex" was about research in the mouse visual system unpicking mechanisms by which neuronal circuits process visual information in the primary visual cortex. Parker's talk "Seeing depth with two eyes: the binocular physiology of 3D space" discussed how understanding depth perception changes our view of how the brain constructs a representation of the space around us.

Read more about their lectures on our blog: **bit.ly/physocblog**

Read the latest press releases from our journals at **physoc.org/news**

Removing our tonsils and adenoids might not be such a good idea

A study of 1.2 million Danish individuals tracked from age 10 (in some cases up to age 30) showed that having either your tonsils or adenoids removed had increased long-term risks of respiratory, infectious and allergic diseases. This means possible short-term benefits need to be stacked against these long-term risks.

DOI: 10.1001/jamaoto.2018.0614

Paralysed people walk again after spinal cord stimulation and physical therapy

Two recent studies restored walking in patients with spinal cord injury. One study restored walking in three men not just in the lab but also outside. Rather than using previously attempted continuous electrical stimulation, researchers applied a pattern of stimulation. Even after stimulation was turned off, people maintained control of their legs, suggesting the connection between brain and spinal cord was re-established. Importantly, it is unclear who will benefit from this therapy as spinal cord injury varies, and accessibility to this expensive and intensive therapy is also limited.

DOI: 10.1038/s41586-018-0649-2

Three peoples' brains were connected, allowing them to share thoughts

Scientists have connected the brains of three people, allowing them to pool their thoughts to play a game of Tetris. The system works through a combination of electroencephalograms (EEGs) for recording the electrical impulses of the brain, and transcranial magnetic stimulation (TMS) which stimulates neurons using magnetic fields. The system detected when a person wanted to rotate a block based on the brain's response as the person stared at one of two flashing lights. The three people completed the task with 81.3% accuracy.

arXiv:1809.08632

Physiology Feed continues on p.15

A later school start trial for adolescent night owls

Julia Harrington

Headmistress, Queen Anne's Secondary School, Berkshire, UK & CEO of BrainCanDo

Students at Queen Anne's Secondary School are fans of a later start time.

There is a growing amount of research on the power of sleep for the optimisation of health and performance in adolescents. An article published in 2016 in *Sleep Medicine Reviews* highlighted some of the impacts that instituting a later start time has had in other schools and we wanted to try it with our sixth-form pupils (Minges & Redeker, 2016). The greatest shift in biological rhythms (i.e. going to sleep later, waking up later, and having higher performance levels later in the day) are often found in older adolescents. Therefore, we chose to work with our year one sixth-form pupils. We understood that the change in the sleep/wake cycle often means that adolescents do not feel sleepy until much later in the evening. This later sleep time then has an impact on how much sleep they are getting in any one night. If we push back the school start time from 8:35 am until 10.00 am, this would provide an opportunity for our pupils to fall asleep at a time when they feel naturally tired and to wake more naturally once they have had enough sleep rather than rely on alarm clocks.

For one week in June 2018 we shifted the timetable for our year one sixth-form pupils. All of the same lessons still took place during that week but they were scheduled to happen at later times throughout the day, such as lunchtimes and others to slots after school. All teaching was finished by 6:15 pm. In effect, this meant that our pupils did not need to arrive in school until much later. For the boarding pupils, breakfast was served at the later time of 9:15 am. We compared this to the control group who started at 8:35 am. They completed the surveys and tasks a week before and a week after the late-start week.

Anecdotally, staff in the boarding house reported that the pupils generally seemed happier and more alert throughout late-start week. Teachers also reported that pupils seemed to be more attentive in their lessons. We also worked with Fran Knight, a sleep expert at the Institute of Education of University College London to help us to measure the impact of this later start time on our pupils. Analysis of the data collected by Knight revealed that during the late-start pupils gained an extra one hour of sleep per night on average (they slept an average of 8 hours per night) and more pupils reported that they were able to wake up without an alarm clock. We also found an improvement in their attention and ability to control impulses, such as interjecting thoughts during a lesson, compared with a typical start time.

> "We also found an improvement in their attention and ability to control impulses during a lesson, compared with a typical start time"

While conducting the trial, we also wanted to raise awareness among our pupils about the importance of good sleep hygiene. Sleep experts Nicola Barclay from the Sleep and Circadian Neuroscience Institute, University of Oxford University and Fran Knight, University College London delivered a lecture for all of our pupils and parents about sleep and the teenage brain. The talk included an explanation of the shifting biological rhythms in adolescence, the impact this has on the sleep/wake cycle and what teenagers could do to practice good sleep hygiene.

All of the staff within the school were extremely supportive of this initiative, from the senior leadership team, parents and pupils through to the teachers who willingly gave up lunchtimes or stayed until later in the evening. We would certainly recommend this practice to other schools, even for a one week trial to highlight the importance of sleep hygiene to pupils. The feedback was overwhelmingly positive. One of the advantages of doing the late-start week is that this provided a platform for us as a school to really raise awareness of the vital role that sleep plays in a range of functions including memory consolidation and learning. We were able to use evidence to really highlight issues around developing good sleep hygiene. The findings from the week have given us much food for thought.

References

Minges KE & Redeker N (2016). Delayed school start times and adolescent sleep: A systematic review of the experimental evidence. *Sleep Medicine Reviews* **28**, 86-95.

Chronobiology Q&A with our journals' Editors-in-Chief

Chronobiology is at the forefront of many researchers' minds. The Physiological Society's 2018 theme is "Physiology of our Body Clocks", there is a Society Meeting called "Sleep and Circadian Rhythms: From Mechanisms to Function", and the 2017 Nobel Prize for Physiology or Medicine was awarded for work elucidating the genetic makeup of the circadian clock.

Following suit with this themed issue, we asked our journals' Editors-in-Chief to weigh in on the impact of chronobiology on physiological research from the perspectives of experimental design and journal policy. We would like to thank Kim Barrett (*The Journal of Physiology*), Mike Tipton (*Experimental Physiology*), and Thomas Kleyman (*Physiological Reports*) for their time and informative answers.

Should journals make providing time-of-day information for all experimental interventions and measurements compulsory? Similarly, do you think light intensities and timing of exposure of animals (to handling for health checks, cage cleaning, adding food etc.) should be reported?

KB: There is increasing evidence that a wide range of physiological processes are influenced by factors such as time of day, as well as light exposure during normally dark periods or feeding periods. We have not yet attained sufficient understanding of the impact of chronobiology on all physiological mechanisms studied by our authors to mandate time-of-day reporting for all studies. However, it would not be unreasonable to encourage such reporting, where relevant.

MT: This is already standard practice in some areas (e.g. human physiology) where you will see statements like "the experiments were conducted at the same time of day to avoid circadian variation." I would leave this consideration to editors and reviewers at present. They should be considering this along with all other possible sources of pre-exposure variation (familiarisation, diet, fluid intake, exercise etc.).

TK: I agree with Mike's and Kim's responses. I would not require that authors address issues related to chronobiology. I think it is reasonable to suggest that authors provide a limited amount of information regarding chronobiology in the methods section, including the timing of the day/night cycle and the timing of studies (day vs. night), where applicable.

Do you think that policy concerning aligning the activity periods of nocturnal animals with times when they are more likely to be visited and handled by animal facility staff and researchers, should be implemented? (Staff and researchers would need night-vision goggles).

KB: This is a tricky one. Experimental outcomes in some studies may be influenced by artefacts introduced when normally nocturnal animals are disturbed during their rest periods. However, there are also health and safety issues to be considered for the staff and researchers, to say nothing of the fact that the animals might be subjected to greater stress and even the potential for injury when they are handled or maintained in the dark (even with the benefit of night vision goggles)! Based on my understanding of the latter, I don't think the technology is currently adequate to allow for appropriate and safe use, particularly when surgical manipulations are planned. The bottom line is that more research is definitely needed.

MT: More studies need to determine the criticality of this aspect. Unanswered questions concern not only laboratory housing but also the choice of animal models and isolation from other factors present in the natural environment e.g. moonlight (Kronfeld-Schor *et al.,* 2013). This question also applies to human studies. For example, should elite athletes preparing to perform in another country (e.g. Tokyo 2020) train at the time of their event in UK time or Japanese time? What about if they go to Japan early enough to adjust their circadian rhythm? There are also limited data to suggest that the timing of acclimatisation is important (Shido *et al.,* 1999) - threshold reductions for the onset of sweating were mostly observed if thermal loading was applied at the same time of day as the original adaptation impulse ("adaptation memory"). Finally, all of our data on humans tend to be collected between 9 am and 5 pm on Monday to Friday. How valuable are these data (e.g. survival time estimations) when a ferry sinks outside of this period?

TK: My impression is that carefully addressing questions related to chronobiology in mammalian systems requires that staff (investigators, postdocs, predocs, techs) be flexible regarding work hours, and be willing to work nights. This is a lot to ask of trainees and technicians, including animal care technicians. Reminds me of when I was training in medicine, and frequently on night call.

References

Kronfeld-Schor N, Bloch G, Schwartz WJ (2013). Animal clocks: when science meets nature. *Proceedings of the Royal Society B: Biological Sciences* **280**, 20131354.

Shido O, Sugimoto N, Tanabe M, Sakurada S (1999). Core temperature and sweating onset in humans acclimated to heat given at a fixed daily time. *American Journal of Physiology* **276**, R1095-101.

Congratulations to our newest Fellow Members

- Mary McGahon, Queen's University Belfast, UK
- Paul Benjamin, University of Sussex, UK
- Munir Hussain, University of Bradford, UK
- George Fink, University of Melbourne, Australia
- Lijun Shang, University of Bradford, UK
- Stewart Sage, University of Cambridge, UK
- Graham McGeown, Queen's University Belfast, UK
- Gordon Lees, University of Aberdeen, UK

Together, physiology and epidemiology can unravel why shift work disrupts circadian rhythm and increases disease risk

Jennifer Ritonja & Kristan J Aronson

Department of Public Health Sciences; and Division of Cancer Care and Epidemiology, Cancer Research Institute, Queen's University, Kingston, Ontario, Canada

Shift work, often including work at night, is an increasingly prevalent work schedule around the globe. For years, disparate researchers such as epidemiologists, chronobiologists, and physiologists have each studied how night work may cause poor health outcomes from their distinct vantage points. We have learned that, acutely, shift work can cause poor sleep quality and sleep deprivation, fatigue, melatonin suppression, and cognitive impairment. Long-term, shift work raises the risk for several health problems including injury, cardiovascular disease, and cancer. But the complete picture of the pathways linking shift work to various health outcomes is not well understood, and could be more rapidly discovered with epidemiologists working in collaboration with physiologists.

The relatively recent discovery of circadian clock genes and the recognition that about 10% or more of our biological functions depend on our synchronisation to an approximately 24-hour clock (called circadian rhythm) are key to understanding the pathways from shift work to increased disease risk.

Circadian rhythm refers to physiological processes and behavioural habits that follow a roughly 24-hour cycle, such as sleep-wake activity and highs and lows of metabolism and blood hormone concentrations. As a diurnal species, our physiological rhythms are naturally timed to coincide with being active during the day and sleeping at night. However, rhythms can be adjusted when we change our sleep-wake patterns, eating patterns, and light exposure. When our physiological rhythms operate outside of the natural diurnal rhythm, transient periods of circadian misalignment or disruption can occur as the system attempts to re-align to the new environmental time cues. It is hypothesised that shift work leads to circadian disruption by misaligning an individual's physiological processes because of exposure to light at night, changed sleep-wake cycles, and altered eating patterns.

Both experimental and epidemiological studies suggest a misalignment of circadian rhythms in shift workers working nights in a rotating or permanent schedule. Night work is related to changes in the level and timing of melatonin and cortisol, disruption of body temperature cycles, changes in sex hormone levels, reduced alertness and psychomotor performance, and reduced heart rate variability. Since the purpose of the circadian rhythm is to synchronise physiological function with the environment, disruption of this rhythm by shift work can lead to sleep deprivation and poor sleep quality, dysregulation of metabolism, changes in hormonal production, as well as maladaptive changes in behaviour (e.g. diet, physical activity) that may promote the development of disease.

Photo by Kristan Aronson

Following our research showing an association between long-term shift work and increased breast cancer risk, our research group is contributing to this area by exploring how shift work affects sleep quality and biomarkers such as melatonin and cortisol (Grundy *et al.*, 2013). In observational studies, female hospital employees working day and rotating night shifts answered questionnaires including their current and past shift work exposure, and were studied over an 8-day period. Sleep and physical activity were measured using accelerometers, and urine was collected over a 48-hour period to measure melatonin and cortisol. The results suggest that working nights on a rotating pattern is associated with lower 24-hour melatonin and cortisol

> "By working together, we hope that new knowledge will be generated to understand causal mechanisms, identify risk factors for shift workers, and inform future workplace interventions and policies"

output, phase shifts in these patterns, poorer self-reported sleep quality, and shorter objectively measured sleep duration (Grundy *et al.*, 2013; Hung *et al.*, 2016; Korsiak *et al.*, 2018; Lajoie *et al.*, 2015; Leung *et al.*, 2016). In addition, our research suggests that cortisol and sleep duration may be intermediates in the pathway linking shift work to cardiovascular risk, including metabolic syndrome (Korsiak *et al.*, 2018; Ritonja *et al.*, 2018). Currently we are assessing differences in light exposure at night, objectively measured by accelerometers, for night and day workers, and investigating the relationship between melatonin patterns and methylation of clock genes.

While our research and other evidence supports a link between shift work and circadian disruption, there are still gaps in knowledge. It is unclear how exactly different aspects of shift work, such as the duration of night work, and the frequency and pattern of night shifts induce chronic circadian disruption. This is made even more challenging by the lack of tools to clearly measure and define circadian disruption and a lack of consideration of chronotype in many observational studies.

In addition, studies are lacking on factors related to circadian adaptation in shift workers (Ritonja *et al.*, 2018): while there is evidence that many shift workers show varying degrees of circadian adaptation to their work schedules, there is no evidence that complete adaptation to shift work is possible. It may be possible for some individuals to adapt to night shift work, by adjusting shift lengths and schedules, changing exposure to blue and bright light, and allowing napping during shifts. However, current evidence on these strategies to promote circadian adaptation is limited.

In order to fully understand the complex pathways linking shift work to circadian disruption and associations with adverse health outcomes, interdisciplinary knowledge from multiple fields is needed to understand the causal mechanisms. We hope that physiologists can collaborate with epidemiologists to investigate how the biological effects of different aspects of shift work, light exposure, changes in sleep times, and changes in eating patterns can impact physiological rhythms.

Most research has focused on melatonin, necessitating the need for studies addressing how cortisol and metabolic biomarkers change in response to circadian disruption. In addition, physiologists can help inform strategies for circadian adaptation by exploring how factors such as chronotype and varying shift schedules may induce circadian misalignment. Finally, new measurement techniques for precise measurement of circadian disruption are needed. By working together, we hope that new knowledge will be generated to understand causal mechanisms, identify risk factors for shift workers, and inform future workplace interventions and policies.

In conclusion, prevalent shift work poses many challenges to the health and well-being of workers in today's society. We recommend greater interdisciplinary collaboration between physiologists and epidemiologists in this exciting and important research area, a collaboration that is essential for fully understanding the impact of shift work and chronic circadian disruption on disease risk.

References

Grundy A, Richardson H, Burstyn I, *et al.* (2013). Increased risk of breast cancer associated with long-term shift work in Canada. *Occupational and Environmental Medicine* **70**(12), 831–838.

Grundy A, Tranmer J, Richardson H, *et al.* (2011). The influence of light at night exposure on melatonin levels among Canadian rotating shift nurses. *Cancer Epidemiology, Biomarkers & Prevention* **20**(11), 2404–2412.

Hung EWM, Aronson KJ, Leung M, *et al.* (2016). Shift work parameters and disruption of diurnal cortisol production in female hospital employees. *Chronobiology International* **33**(8), 1045–1055.

Korsiak J, Tranmer J, Day A, *et al.* (2018). Sleep duration as a mediator between an alternating day and night shift work schedule and metabolic syndrome among female hospital employees. *Occupational and Environmental Medicine* **75**(2), 132–138.

Korsiak J, Tranmer J, Leung M, *et al.* (2018). Actigraph measures of sleep among female hospital employees working day or alternating day and night shifts. *Journal of Sleep Research* **27**(4), e12579.

Lajoie P, Aronson KJ, Day A, *et al.* (2015). A cross-sectional study of shift work, sleep quality and cardiometabolic risk in female hospital employees. *BMJ Open* **5**(3), e007327.

Leung M, Tranmer J, Hung E, *et al.* (2016). Shift work, chronotype, and melatonin patterns among female hospital employees on day and night shifts. *Cancer Epidemiology, Biomarkers & Prevention* **25**(5), 830–838.

Ritonja J, Aronson KJ, Day AG, *et al.* (2018). Investigating cortisol production and pattern as mediators in the relationship between shift work and cardiometabolic risk. *Canadian Journal of Cardiology* **34**(5), 683–689.

Ritonja J, Aronson K, Matthews R, *et al.* (2018). Individual differences in shift work tolerance and recommendations for research and practice. *Industrial Health (In Press).*

Vaginal seeding of newborns doesn't actually work

Babies delivered by C-section and thus avoiding vaginal microbial inoculation have different microbiomes and thus appear to be at a greater risk of developing problems like asthma, allergies, autoimmune disorders, and obesity. Despite the fact that vaginal seeding has gained popularity, there is no convincing evidence that it is either effective or safe. The difference in infant microbiomes is more likely to be caused by antibiotics administered to mothers who have undergone a C-section.

DOI: 10.3389/fmed.2018.00135

Gut and brain are shown to be directly connected through neural circuit

We already know that the gut talks to the brain via hormones in the bloodstream. This new research suggests a more direct connection via the vagus nerve, a route that doesn't involve the spine. These findings could lead to new treatments for obesity, eating disorders, and even depression and autism.

DOI: 10.1126/science.aau9973

Healthy mice born from same-sex parents have their own offspring

Pups created from two mouse mothers matured and had their own offspring. Only 14% of embryos were viable, and we don't know if the offspring are more prone to diseases throughout their lives. Baby mice produced from the genetic material of two fathers, on the other hand, only lived for a few days.

DOI: 10.1038/d41586-018-06999-6

In-body gene editing seems safe but effectiveness is unclear

Researchers designed enzymes to correct an error in the genome of people with the rare genetic disease that prevents sugar breakdown, called Hunter syndrome. The treatment reduced levels of a biochemical marker used to assess severity of the syndrome. However, it is unclear whether the therapy worked as the researchers didn't detect an increase in the enzyme missing in the patients.

DOI: 10.1038/d41586-018-06195-6

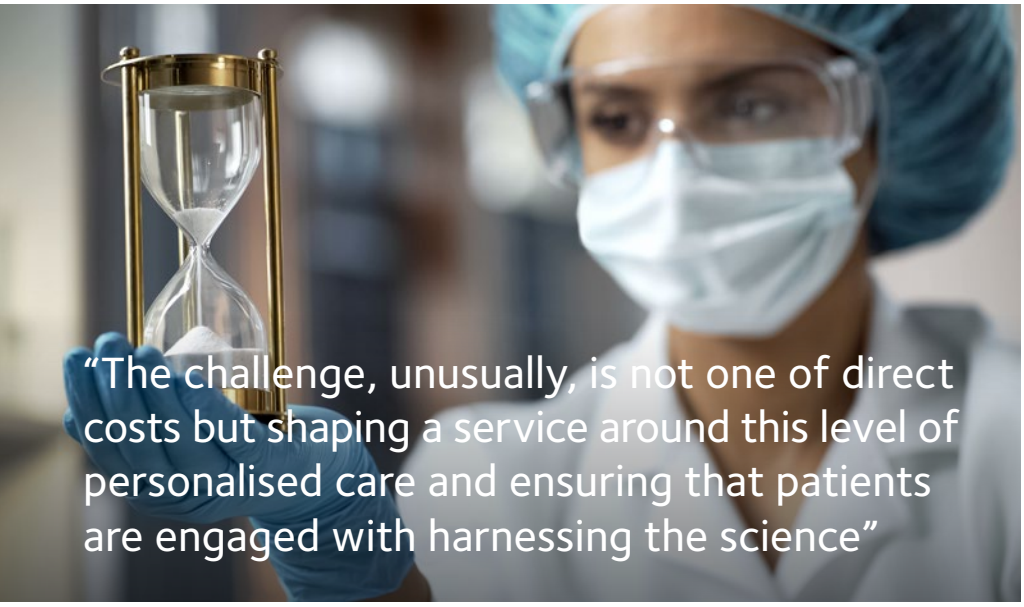
Physiology Feed continues on p. 19

Has chronotherapy arrived just in time?

Tom Addison

Policy Manager, The Physiological Society

The time sensitive nature of health interventions is a concept that is well understood by health policymakers and, increasingly, the public. The cost of "avoidable illness" is highlighted as a priority in the NHS *Five Year Forward View* and recognises that improved long-term well-being and early intervention are crucial for managing the demands on the health service. More broadly, the impact of time (in this case, the day of the week a patient is admitted) on survival rates in hospitals also made the news during the 2015 General Election campaign when the Conservative government promised a 'Seven-day NHS'.



The health system is also increasingly focused on a patient-specific approach to medicine with the emergence of personalised medicine, which recognises that diseases (and their treatment) involve a "complex interaction of our biological make-up and the diverse pathological and physiological processes in our bodies" (NHS England, 2016). In essence, policymakers appreciate that the era of "silver bullets" is at an end.

The positive therapeutic benefits of time, however, are less well understood by policymakers despite a growing body of evidence across life sciences of the benefit of timing diets and medical treatment with the body's natural circadian rhythm that dates back to the 1960s. Last year's Nobel Prize for Physiology or Medicine was awarded to three researchers who discovered the molecular mechanisms controlling the circadian rhythm. Despite hints that chronotherapy could be beneficial in treating a number of forms of prevalent cancers, a survey, published the year before the 2017 Nobel Prize was awarded, found that only 0.1% of ongoing clinical trials incorporated time-of-day considerations into their analyses (Selfridge *et al.*, 2016).

The lack of research that has made it to the stage of clinical trials is at odds with the likely traction that this field of science would generate with policymakers and the general public. Interest would likely be driven by three factors: financial burden (or lack thereof), simplicity of the argument, and the NHS' focus on technology.

To the first point, superficially at least, chronotherapy will appear like something for nothing. Policymakers understand the value of other forms of personalised medicine but associate these with a substantial financial burden that will need to be met by a public system but will not necessarily generate uniform outcomes across patients – some very expensive drugs will have no benefit for certain patients depending on their genetic make-up. Crudely put, everyone has a circadian rhythm and chronotherapy is currently focused on using existing (and approved) therapies more effectively rather than segmenting patients.

Secondly, chronotherapy is straightforward to explain and, as touched on above, fits within the public's existing scientific understanding. The public can describe how something like exercise or eating makes them feel at different times of the day. Transposing this knowledge into the field of medicine should (in theory!) therefore be straightforward.

Finally, chronotherapy fits comfortably within the new Health Secretary's drive to use technology to ease the burden on the NHS. A blood test to check the synchronicity of a patient's body clock could be administered at home and technology used to alert patients to the need to take medication at the most effective time of day.

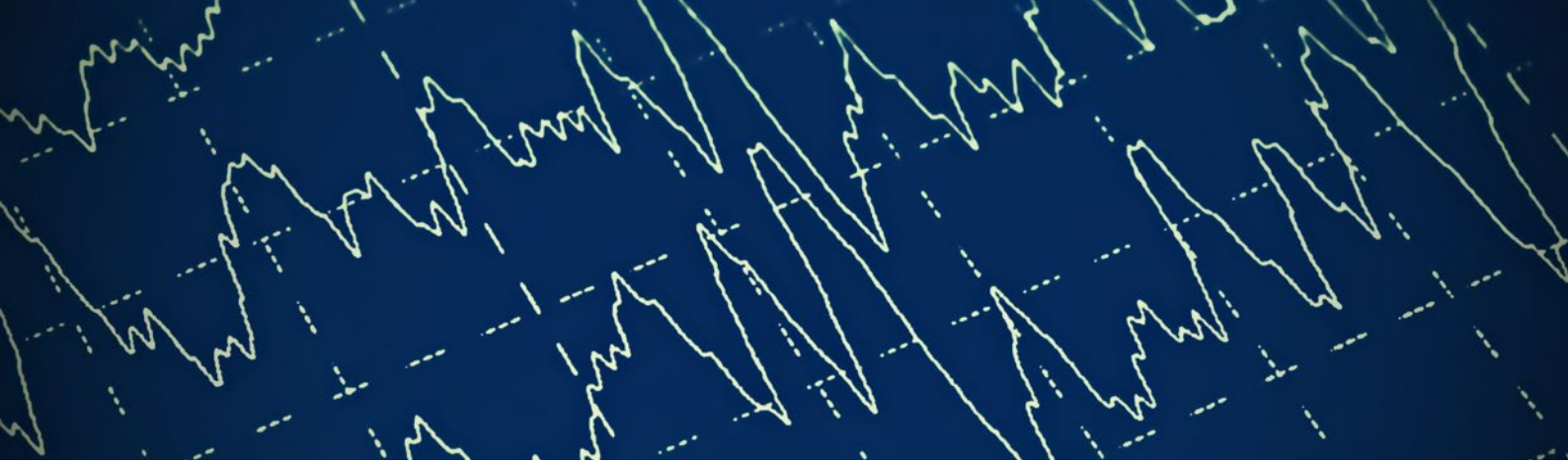
The challenges for policymakers are two-fold. Should research prove the value in chronotherapy, reorganising healthcare systems to accommodate the circadian rhythm of individuals has the potential to be a huge administrative task given the often sizeable delay between diagnosis and beginning treatment. On a related note, one of chronotherapy's biggest benefits could also become a challenge. The number of conditions and patients that might benefit could be enormous. As just one example, 41,000 people are diagnosed with bowel cancer in the UK every year.

Chronotherapy is an exciting field of study for policymakers and the public alike given its potential to improve efficacy, or at least lower toxicity, at a negligible financial cost to the health system. The challenge, unusually, is not one of direct costs but of shaping a service around this level of personalised care and ensuring that patients are engaged with harnessing the science to maximise its benefits.

References

NHS England (2016). Improving outcomes through personalised medicine: Working at the cutting edge of science to improve patients' lives. Available at: https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf.

Selfridge, JM *et al.* (2016). Chronotherapy: Intuitive, sound, founded...but not broadly applied. *Drugs* **76**, 1507–1521.



Time to learn: The teaching of circadian rhythms

Edward Hayter

University of Manchester, UK

The importance of circadian rhythms has gained widespread recognition recently since the 2017 Nobel Prize in Physiology or Medicine was awarded to circadian biologists Michael Young, Michael Rosbash and Jeffrey Hall for determining the molecular mechanisms of the clock in fruit flies. Indeed, several UK institutions now have substantial research groups focusing on circadian rhythms and related processes (such as Manchester, Oxford and Surrey). The rapid growth of this field, coupled with its ubiquity across species and disciplines, begs the question of when, and to whom, it should be taught.

Some universities across the UK, including Warwick, UCL, Surrey, Oxford and Manchester, have begun teaching circadian rhythms as an optional undergraduate module aimed at final-year students, though the availability of these units depends highly on the degree program. For example, Warwick and UCL offer their courses primarily to life science students with the aim of understanding the science behind circadian rhythms, while Surrey also offers the unit to more applied courses, such as Nutrition and Sport and Exercise Science, to communicate the importance of circadian rhythms in health and disease. Oxford shares this attitude and offers their unit to students reading Medical and Biomedical sciences to make students aware of the real-world impact of circadian rhythms and chronotherapeutics/pharmacology in treating disease.

As the importance of circadian rhythms in everyday life and disease states is becoming increasingly apparent, I believe this discipline, especially the idea of chronopharmacology, should be a fundamental concept taught to students training for medical professions. Such teaching would help future medical practitioners provide useful advice about relatively simple changes (such as the time a drug should be taken) that could make a huge impact on patient welfare and outcome. For example, chemotherapy treatments, when administered at the most appropriate time of day, cause significantly reduced side effects.

As a Manchester graduate, I completed the "Clocks, Sleep and the Rhythms of Life" module during my final year. This unit is open to all life science degree programmes but is mostly taken by Neuroscience, Biology, and Pharmacology students. Lectures focus heavily on the neural mechanisms of circadian rhythms, arousal, and metabolism and how they integrate to control whole animal behaviour and physiology. They also highlight the impact of the circadian system on cognition and sleep. Overall this was one of the most enjoyable units during my time as an undergraduate, due in part to the wide range of physiological systems that are influenced by the circadian system and the requisite integration of contemporary research into the teaching. The course certainly helped me become more engaged in the topic and ultimately led to me pursuing a PhD in the field.

Interestingly, some students are exposed to teaching on circadian rhythms even earlier than undergraduate level. Biological rhythms are briefly included in the AQA and OCR (two main UK exam boards) A-level Psychology syllabi, including information on what they are and how they are involved in shift-work/jetlag (OCR) and circadian pacemakers and entrainment to external stimuli (AQA). At the other end of the spectrum, medical students, postgraduates or early career researchers who have not learned about circadian rhythms, or wish to supplement their knowledge, can attend the Oxford Chronobiology and Sleep Medicine Summer School, a 5-day intensive course designed to provide the fundamentals and applications of circadian research.

While teaching of circadian rhythms is becoming more mainstream, should universities be doing more to integrate this topic into the syllabus of life sciences/medical degree programmes? Tim Brown, the unit director for the "Clocks, Sleep and the Rhythms of Life" module at Manchester, says, "Teaching circadian rhythms is especially beneficial because of their prevalence across biology. On one hand, students learn important concepts that will be relevant to any future career in life sciences or medicine.

"The rapid growth of this field, coupled with its ubiquity across species and disciplines, begs the question of when, and to whom, it should be taught"

On the other hand, the direct impact of circadian rhythms on our own day-to-day lives helps students engage with their course in a way that they may not with other topics they are taught." Across the pond, UC San Diego's Centre for Circadian Biology run an integrative project between undergraduates from various disciplines and circadian researchers called the BioClock Studio. This innovative project produces educational resources centred on circadian biology, aims to promote understanding of circadian rhythms, and is targeted towards multiple audiences including students, clinicians, non-circadian researchers, and the general public. This outward-facing initiative is exactly what the field needs to increase accessibility and further promote the importance of biological timing. While progress is being made in this area, innovation like this would really help to accelerate the integration of circadian rhythms into mainstream degree programmes.

The intersection of light, dark, physiology, and architecture

Michael D White

Previous Senior Lighting Designer at Schuler Shook Theater Planners & Lighting Designers, Minneapolis, USA

Few events have had greater impact on our species than the development of artificial light. Lifestyles changed dramatically as a result of this invention, including when we sleep, wake, eat, work, and play. Widespread rapid adoption of electric light occurred with the industrial revolution. It allowed the workday to be independent of night time and the seasons. Subsequently, the advent of fluorescent light, along with elevators and air conditioning allowed us to construct buildings that are tall and wide and have little natural light. Nowadays, most people spend around 90% of their time indoors, and the use of light at night has increased as well. The pattern of light and darkness in the modern world is quite different from the light-dark cycle under which life evolved. From the perspective of an evolutionary timescale, these changes have been essentially instantaneous and the effect on health has been profound.

Figure 1. In a typical patient room, the bed faces the corridor. Behind the bed to the right are windows to the outdoors. The door to the toilet room can be seen above the headboard. The caregiver station is left of the bed, with a charting station and a worktable.

"The pattern of light and darkness in the modern world is quite different from the light-dark cycle under which life evolved"

Chronobiology informing design

Scientists have been connecting the dots from circadian circuitry in the eye to the master clock in the brain to rhythmic gene expression in every cell and rhythmic physiological processes such as melatonin secretion and sleep. Moreover, elucidation of the differential impact of light spectra, light intensities and times of exposure, and previous light history has informed design. Knowing how an individual's light/dark exposure affects health and behaviour has allowed architectural lighting designers to integrate light in architecture for health. An understanding of the cause and effect allows us to develop innovative solutions. At the University of Minnesota Masonic Children's Hospital in Minneapolis, Minnesota, I was part of a team that implemented a lighting and controls system in a paediatric intensive care unit. The design intent was to use light and darkness to positively affect patient outcomes.

In a hospital room, every item is planned with respect to size, colour, finish, and location (Fig. 1). There are three sources of light – overhead, from the window, and from computer screens. Over the bed is the requisite four-lamp fluorescent light, which produces a field of bright light, needed during examinations and medical procedures. While this satisfies the code requirement, the glare it produces is unacceptable, so the fixture is typically switched off. As the windows are approximately 15 feet (4.57 metres) behind the patient, little natural light reaches the patient's eyes. At night there is a glow of light from the corridor and computer screens.

The overall result is a kind of 24/7 twilight punctuated by periods of bright light at random times. This is an extreme environment where patients receive no environmental cues to indicate day or night, and worse, they get false cues from the exam light. They have difficulty sleeping and often slip into delirium or depression which negatively affects their health and makes treatment more difficult.

As part of a continuous development programme, the hospital engaged a design team to create an environment that would resolve these issues. Together, we developed a set of objectives to guide the process.

Objective 1: Maximise brain and body rest using maximal darkness exposure

The first design task was to design the darkness. This was the hardest objective to achieve because it is beyond the scope of normal consideration - designing darkness is a novel concept. Nonetheless, we used improved drapery to shield against light spilling from the family area and the corridor. We also eliminated windows that open onto adjoining rooms. Understanding that caregivers must have light to do their work, we developed specific control settings for use at night so that patients are exposed to as little light as possible. With all elements in place, the minimum intensity measurement

was 5 lux (a measure of light intensity on a given surface). Whilst good, the ideal would be closed to 1 lux, which is the intensity of a full moon. The overall intent is to provide an extended period of darkness so that melatonin is released into the patient's bloodstream and vital night-time processes can occur.

Objective 2: Synchronise timing of wake/sleep onset to developmental age using the first two hours and last two hours of light

The fixtures over the bed have colour-tuning capability, meaning that the quantity and spectral output can be controlled. This allowed automatic delivery of a carefully controlled dose of light to the patient between 8 am and 10 am in the morning. The dose was calibrated to deliver enough light at the eye to stimulate our master clock, the suprachiasmatic nucleus, suppressing the production of melatonin, and beginning the cascade of physiological events that normally happen during the day (Lucas *et al.,* 2014).

During the hour prior to bedtime, the quantity of light in the room is slowly reduced and the blue part of the spectrum is removed. The intent is to prepare the patient for sleep by restricting exposure to light. The timing of this change depends on the age of the patient. The young children go to sleep at 6 pm, while teenagers can stay up until 10 pm.

Objective 3: Liberalise light use during middle of the day, within limits; maximise alerting during engaging activity, minimise light exposure during rest

The system is designed to allow patient control over the lighted environment. Using a touch screen mounted on a boom-arm, the patient can control the system for most of the day. The lighting overhead and on the wall wash can be adjusted for colour and intensity (minimum 10 lux during the daytime). The light can be warm or cool, bright or dim. Programmed sequences are available that suggest rainbows, fireworks, or northern lights. We also developed lighting sequences that play in conjunction with a series of lullabies, composed by music therapists. The light and sound sequences help patients relax and get to sleep.

A controlled study of effect of light and darkness on patients is planned. Initial anecdotal evidence from caregivers is positive, and they are assigning some of the most critical patients to the three rooms with the new system.

References

Lucas RJ, Peirson S, Berson DM, Brown TM, Cooper HM, *et al.* (2014). Measuring and using light in the melanopsin age. *Trends in Neurosciences* **37**(1), 1–9. https://doi.org/10.1016/j.tins.2013.10.004

Figure 2. The new lighting and control system is an immersive environment that projects the hospital's warm and caring mission, while improving patient outcomes.

Peer reviewing at study protocol stage reduces publication bias towards positive results

Pre-registering and peer-reviewing studies before research was conducted meant null findings were much more likely to be reported. Around 140 journals currently use this format worldwide.

DOI: 10.1038/d41586-018-07118-1

Google launches new searchable repository of datasets

Dataset search pools data across disciplines, including scientific, government and news-related data. To enable users to locate data, they encourage anyone who publishes data online to use certain guidelines to describe their data.

bit.ly/2DF8dWx

Flu Protection 2.0 – offering protection against several strains in mice

Potent flu strains kill as many as 646,000 people worldwide each year. To more effectively curb the disease, researchers have created an antibody that works against 59 strains. It does so by targeting a ubiquitous region of the flu virus, rather than strain-specific heterogeneous regions.

DOI: 10.1126/science.aaq0620

Big data about the brain made available on web service NeuroData

20 trillion voxels' worth, or several terabytes of imaging data are now available on a free, cloud-based platform called NeuroData. The data is spatially organised so you can retrieve images from any section of the brain and send links to these particular visualisations.

DOI: 10.1038/s41592-018-0181-1

This little-known STD could become the "next superbug" within a decade

Sexual health experts warn that *Mycoplasma genitalium* has the potential to become a drug-resistant superbug within a matter of years. More common than gonorrhea, if left unchecked *mycoplasma genitalium* could result in thousands of women each year at increased risk of infertility.

bit.ly/2Ol55QS and bit.ly/2nosWE9

The trouble with stumbling upon circadian clocks

Anne-Marie Neumann

Institute of Neurobiology, Center of Brain, Behavior & Metabolism, University of Lübeck, Germany

Circadian systems play a crucial role in the physiology and health of living beings, adapting processes to the 24-hour light-dark cycle of the Earth. Although around 50% of mammalian genes present circadian oscillations, the concepts of circadian rhythms are rarely established in research groups other than those specifically focused on clocks and rhythms (Zhang *et al.,* 2014). As a PhD student specialising in neuroscience and working on behavioural and metabolic rhythms after weight-loss surgery, I firmly believe non-consideration of biological rhythms is a major shortcoming of many scientific studies. This may be due to persisting gaps in chronobiological training at universities and a general lack of its awareness in parts of the biomedical community.

As for most people, I grew up with chronobiological advice like "Do not eat too late!" and "Disrupted sleep is unhealthy!", and encountered the phenomena of jet lag and inner clocks. Despite this, contact with rhythms and clocks in a scientific way required travelling across the globe. I did not come across the term "circadian clock" until I attended the Neuroscience 2014 conference in Yokohama and listened to a lecture by Paolo Sassone-Corsi - a prominent researcher in the circadian clocks field with a specialty in epigenetics and metabolism. In combination with a growing interest in behavioural biology his talk struck a chord.

Unfortunately, maybe due to a lack of research groups investigating molecular mechanisms underlying psychiatry and behavioural rhythms in northern Europe, it took a while after graduation to find a PhD position covering my newly discovered scientific passions. And only now do I fully grasp the importance of rhythms and proper timing of experiments in science. In my previous studies, I never considered whether testing at another time point may change experimental outcomes, but with my broadened awareness and knowledge today, I will keep a chronobiological perspective no matter the field I will work in in the future. I think, if you are once a chronobiologist, you will always be a chronobiologist. Even some small exposure to the field for young scientists and medical trainees could pay dividends in terms of integrating chronobiology into domains where it has not been previously considered.

Despite the importance of such an integral system, without professors or readers investigating the topic themselves, chronobiology appears to be neglected. When taking a brief look into textbooks this comes as no surprise: "circadian rhythms" are granted 4 pages out of 979, 10 out of 980, and 9 out of 469 in standard physiology (2017), neuroscience (2016), and endocrinology (2014) textbooks, respectively (Schmidt *et al.,* 2017; Bear *et al.,* 2016; Kleine & Rossmanith, 2014). The topic still needs to thoroughly arrive in textbooks; all junior (and senior) academics should, at least, stumble upon it.

The biology of circadian clocks was not taught during my medical biotechnologist undergraduate training despite mandatory year-long lecture series on general physiology, neuroscience, and their applications in medicine. To the best of my knowledge, medical training similarly lacked teaching of chronobiology. Since then, changes in academic personnel has helped establish the field within the psychiatry department at my Alma Mater and will inevitably promote teaching chronobiology therein.

Currently in Lübeck, circadian clocks are taught to different medical science programmes within a wide-ranging bachelor's physiology series and within a master's neuroscience course. The physiology course mostly discusses the molecular aspects of circadian timekeeping, while the neuroscience course covers more ground, elucidating the interaction of clocks with various brain functions – from memory formation to appetite regulation. Additionally, a laboratory practical week is offered for master's students. A single professor focusing on chronophysiology on site was teaching all of these courses. The topic clearly inspires: every year students have joined the group after that week for their Master's projects and even PhDs. Moreover, within my international research training group only a handful of PhD students heard of circadian clocks during their respective Master's programmes. Today, they are all acknowledging its relevance for science; most have started to consider including certain aspects in their work.

Circadian clocks should be of major interest for everyone studying processes with underlying biological rhythmicity: physiologists, neuroscientists, biochemists, nutritionists, immunologists, endocrinologists, pharmacologists and so on. To understand the complexity of chronobiology, a few lecture hours may not be enough, but should definitely be the minimum. Additionally, specialised courses and summer schools accessible for students not already working in the field, as well as workshops at young researcher meetings may be a step in the right direction.

Luckily, circadian clock research gained a boost of attention due to the awarding of the 2017 Nobel Prize in Physiology or Medicine to Jeffrey C Hall, Michael Rosbash and Michael W Young for discovering the molecular mechanisms controlling the circadian rhythm. In addition to the recurring discussions in many European countries about whether daylight-saving time is still needed, chronobiology became more attractive for students and postgrads alike.

This trend should be used to further anchor circadian biology within all kinds of medical and natural science courses. Young physiologists need to be encouraged to include circadian aspects in their experimental designs. Hopefully, this will lead to more awareness among scientists and, consequently, better education and research. Moreover, patients could greatly benefit from improving and implementing knowledge of best drug dosage timing, impact of chronotypes on treatment outcomes, healthy hospital lightning conditions and synchronisation of scheduled surgeries with biological rhythms. Overall, chronobiology should be seen as fundamental for physiologists and physicians alike.

References

Bear MF, Connors BW, Paradiso MA (2016). *Neurowissenschaften: ein grundlegendes Lehrbuch für Biologie, Medizin und Psychologie.* 3rd edition. Andreas K. Engel (ed.). Berlin Heidelberg, Springer Spektrum.

Kleine B, Rossmanith WG (2014). *Hormone und Hormonsystem: Lehrbuch der Endokrinologie.* 3rd edition. Berlin, Springer Spektrum.

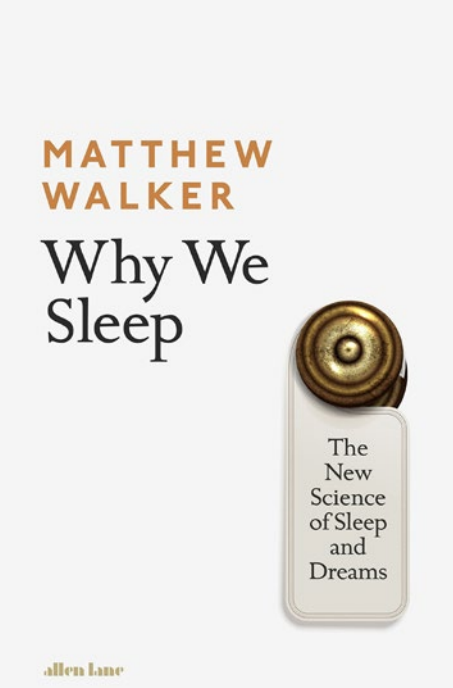
Schmidt RF, Lang F, Heckmann M (2017). *Physiologie des Menschen: mit Pathophysiologie: mit Online-Repetitorium.* Limited Reprint 31st edition. Berlin: Springer.

Zhang R, Lahens NF, Ballance HI *et al.* (2014). A circadian gene expression atlas in mammals: Implications for biology and medicine. *Proceedings of the National Academy of Sciences of the United States of America* **111** (45), 16219–16224. Available from: doi: 10.1073/pnas.1408886111.

Book review:

Why We Sleep by Matthew Walker

Christopher Torrens
University of Southampton, UK



Matthew Walker
Penguin: reprint edition, 2018
ISBN: 9780141983769

Sleep is detectable in every animal studied, from insects to worms to humans and even sharks – despite what you may have heard elsewhere. Nevertheless, our understanding of sleep as a biological process has remained relatively mysterious compared with advances in our understanding of disease processes and other key requirements for life such as eating and reproduction. Recently we have been starting to lift the veil of night from sleep, and in his book *Why We Sleep*, Michael Walker gives a state-of-the-union address on our current understanding.

The scope of the book is huge. It covers topics from circadian biology, dreams, and the impact of a lack of sleep, right up to proposing solutions to cope with such problems on a societal level. Each section is explained clearly and supported by evidence, either experimental or epidemiological data, without ever becoming too in-depth for the non-specialist or too superficial for a physiologist (or at least this one). Despite the easy tone of the writing, this book reads more like a lay textbook than other popular science texts. I say this because it is, quite intentionally, set out to be read either from cover to cover or by cherry-picking chapters in whatever order you choose. Having done bits of both, I can attest that it does little to change the impact or the message conveyed.

What this book does not do is answer the question of why we sleep. When the eminent sleep researcher who initially characterised the five stages of sleep, William Dement, was asked such a question, he replied; "As far as I know, the only reason we need to sleep that is really really solid is because we get sleepy."

What this book provides is lots of evidence of the consequences of a lack of sleep on our health and well-being. Some such consequences are well known. The number of road-traffic accidents attributed to tiredness is greater than the number attributed to drink and drugs combined. However, there are far more subtle things going on here. Poor sleep is associated with increased rates of coronary artery disease, and adults in their 40s who sleep fewer than 6 hours per night are 200% more likely to suffer a stroke or myocardial infarction in their lifetime compared to those who get the recommended 8 hours of sleep. Similarly, reducing sleep to 5-6 hours per night disrupts leptin and ghrelin signalling, leading to increases in food intake and is equally associated with increased blood glucose levels and rates of diabetes. A reduced immune response, higher rates of infection, cancer, depression, schizophrenia, Alzheimer's disease, dementia and infertility are all associated with reduced amounts of sleep.

"Despite the easy tone of the writing, this book reads more like a lay textbook than other popular science texts"

What can be done? Walker does suggest 12 helpful tips for individuals to help improve their own sleep hygiene and also reports on companies trying to change attitudes. Given the questionable decisions made by people who are sleep-deprived, he questions the esteem that we afford people responding to emails at all hours of the day and notes that companies are starting to provide more flexible working and even "sleep pods" and "shhhh zones". On reading this I could not help but think of Homer Simpson asking Hank Scorpio where he could obtain some business hammocks; that was first aired in 1996 so they were both well ahead of the curve on this one.

Packed, as it is, with a mixture of information and practical advice this is a thoroughly interesting read, whether read cover to cover or picked through over time. My most ringing endorsement of this book is that it has given me food for thought and prompted me to make some change to my own sleep patterns. As a night owl living amongst a family of morning larks, I'll have an early start in the morning, so it is time for me to go and get some much-needed sleep.

Fighting media misreporting: A case study in diet and exercise

Robert Edinburgh, James Betts & Javier Gonzalez

Department for Health, University of Bath, UK

Physiology research can provide insights into the mechanisms of disease and potential counteractive strategies (such as diet and exercise). For the majority of people living in developed countries, the information about diet and exercise that is most readily available is not peer-reviewed journal articles, but reports in newspapers and health magazines.

We spend hours obtaining funding and ethical approvals, collecting and analysing data, and writing manuscripts. When our research receives media attention, and the associated results are made accessible in newspapers, blogs and magazines, it is thus, extremely gratifying, as this can help to achieve more widespread impact.

However, even when this goal is achieved, the results from our work can be misreported, resulting in inaccurate and often confusing health messages. This inaccurate reporting of research by the media likely stems from a desire for high-impact messages, which appeal to a "quick-fix" attitude to health. However, non-academics can then understandably become confused and disheartened due to a lack of consistency in health advice. Not only does this lead to the potential for the inappropriate application of the findings, it can also reduce public trust in science and researchers. As obesity and associated cardiometabolic diseases are increasingly prevalent, this represents an especially big problem.

Our group recently published a peer-reviewed article that received media attention (Edinburgh *et al.*, 2018). Whilst many media reports were accurate, some (in widely read newspapers) inferred conclusions from outcomes that were not even measured. Our research made no inferences about body composition, yet the results were spun by some reporters into a new strategy for achieving weight loss (Fig. 1). To reduce the risk of media misreporting, we propose these five tips:

1. **Ensuring that abstracts are clear and entirely reflective of the study results**
   For studies in diet and exercise, this includes being cautious about short *versus* longer term changes or adaptations. The abstract is likely to be the most widely read section of an article (by non-academics), so this may reduce the likelihood of any misinterpretation. Including "new and noteworthy" sections with a focus on how the research is applicable to the public (or target audience) may also help, and is especially important if the journal does not offer open access to the complete article.

2. **Writing two abstracts, one for academics and one lay summary for the public**
   The lay abstract could also be combined with infographics and diagrams to further explain the results to non-academics (Fig. 2).

3. **Working closely with press offices at universities to ensure that the message provided to the media is clear and accurate**
   Carefully writing our own news releases and engaging with opportunities for follow-up questions and interviews helps ensure that media reports will be accurate.

4. **Organising regular public engagement events and engaging with social media**
   Setting aside time for engaging with social media to disseminate findings, engage directly with the public's questions, and respond to inaccurate articles can also increase public trust towards researchers.

5. **Increasing the time allocated to teaching students to be critical of what they read (in newspapers and journal articles)**
   Teaching young people to form their own opinions based on available evidence may be the most powerful longer-term solution to media misreporting (Gonzalez, 2018).

In addition to the many hours we spend performing research, we should allocate more time to ensuring that the message received by the public is always accurate. This relatively small investment may allow our research to have the greatest possible impact.

"This inaccurate reporting of research by the media likely stems from a desire for high-impact messages, which appeal to a "quick-fix" attitude to health"

References

Edinburgh RM, Hengist A, Smith HA *et al.* (2018). Pre-exercise breakfast ingestion versus extended overnight fasting increases postprandial glucose flux after exercise in healthy men. *American Journal of Physiology-Endocrinology and Metabolism.* doi: 10.1152/ajpendo.00163.2018

Gonzalez JT (2018). Using misleading online media articles to teach critical assessment of scientific findings about weight loss. *Advances in Physiology Education* **42**, 500-506.

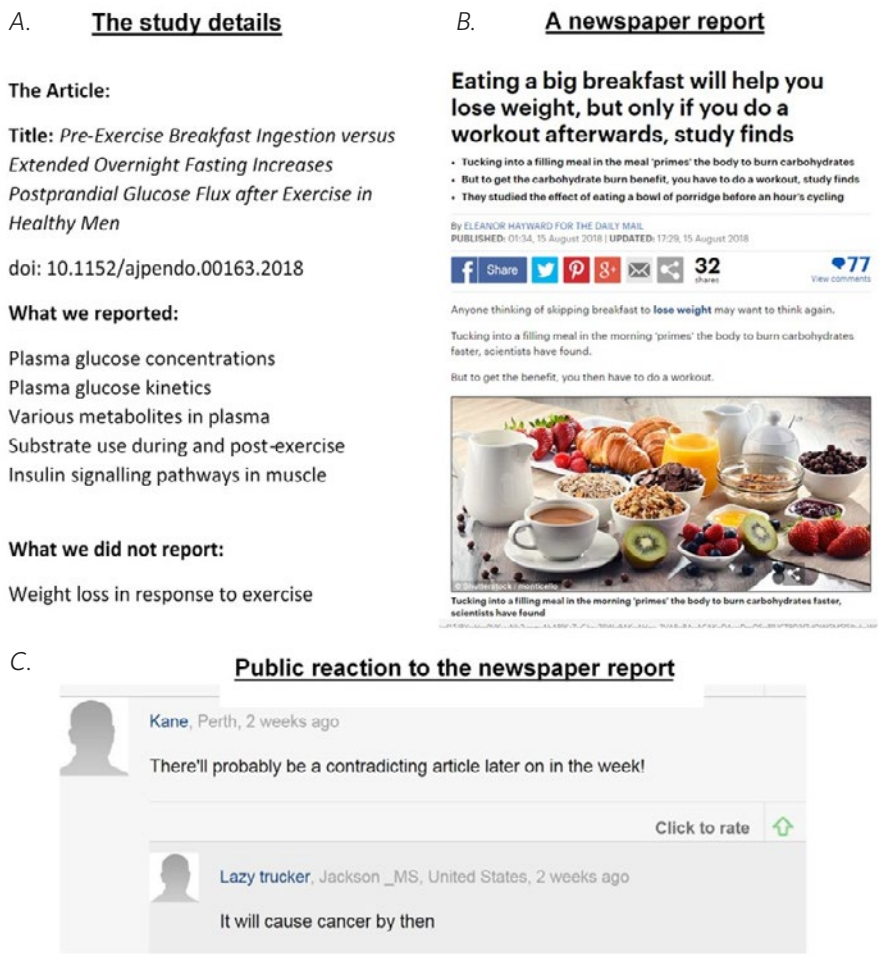


Figure 1. An example of misreporting by the media, whereby the study findings (A) were inaccurately reported by a newspaper (B). This leads to comments from the public suggesting confusion and evidence of erosion in trust towards researchers (C).

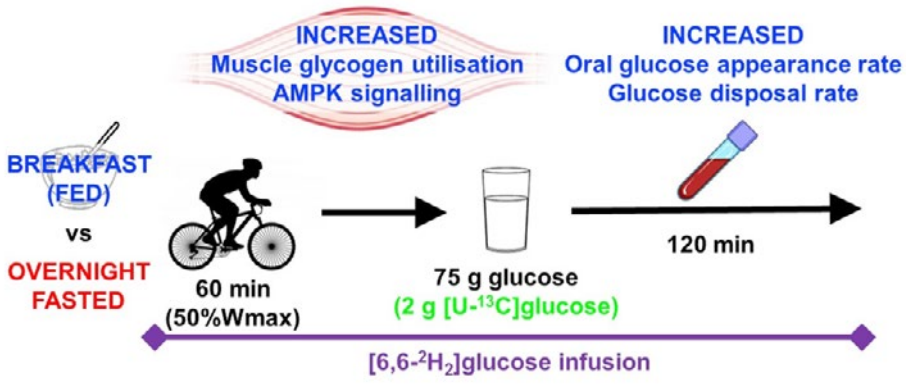


Figure 2. An example of an infographic (relating to the research described in Figure 1). Infographics and similar images could be published alongside a lay summary/abstract.

Read the latest press releases from our journals at **physoc.org/news**

Smoking during pregnancy increases the likelihood of your baby becoming obese

Breakthrough in treatment of Restless Legs Syndrome

Childhood exercise can reverse negative health effects caused by father's obesity

Stress protein could be used to prevent childhood obesity in males

Your genes determine how your heart rate responds to exercise

Lessons from Everest's Sherpas could aid intensive care treatment

Simple leg exercises could reduce impact of sedentary lifestyles on heart and blood vessels

Shivering in the cold? Exercise may protect against muscle fatigue

Ketogenic diets may lead to an increased risk of Type 2 diabetes

Eat high fibre foods to reduce effects of stress on gut and behaviour

Use of nicotine during pregnancy may increase risk of sudden infant death syndrome

High intensity exercise in teenagers could ward off heart disease

Oxygen therapy could help combat dementia in individuals with lung disease

Exercise makes the blood of obese people healthier

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

The President, Bridget Lumb, welcomed new Trustees David Paterson (as President-elect), Matt Taylor (as the External Trustee) and Raheela Khan (as the Elected Trustee) to their first meeting of Council.

Council discussed Europhysiology 2018 and was pleased to note that it had been a great success in terms of the scientific programme, the education programme and networking opportunities. Council was looking forward to receiving a more detailed assessment of the event and would be looking to build on the successful elements. The Director of Scientific Programmes (Simon Rallison) reported that approximately 64% of attendees were not Members but some quantitative evaluation would be undertaken.

The main point of business at the October meeting of Council was the Governance Review. Governance Consultant, Lucy Devine (Director of Wellspring Consulting) gave an update on the Governance Review process so far, including the background and timeframes of the project to date and summarised the outcomes of the workshop session from the previous day. She noted that the draft recommendations had been developed based on feedback from Trustees and staff and that any future structure should: reflect the strategy, remove duplication, enable agility, engage a wider cohort of Members in activities, remove stagnation of composition and engage with external experts.

Council was open to the structure in principle and requested that a fully worked up proof of concept be developed. This would be reviewed by the Governance Working Group and their recommendations taken to Council in December.

An update was given on our property and following a recommendation from the Property Strategy Working Group and the findings of the Charity Report (which was provided by Mann Smith & Partners, RICS surveyors), Council approved the tenancy lease for the second floor of Hodgkin Huxley House.

Council received a paper from the Chief Executive Officer (Dariel Burdass) and Simon Rallison on Innovation and Income Diversification. Trustees noted their responsibility for future proofing The Society and the threat to the stability of subscription journals from open access (and particularly Plan S). It was also noted that while The Society had healthy reserves, and could look at ways to reduce operating costs, Council agreed that it should consider alternative methods of income diversification. This would be considered again in 2019 following a review of the Reserves Policy.

The Head of Professional Development and Engagement (Chrissy Stokes) highlighted the new version of The Society's career resource, Understanding Life, which was created in time for Physiology Friday. This was an amalgamation of two resources and had been evaluated with the target audience of undergraduates but was also popular with 16 – 19 year olds. The resource provided information about the definition of physiology and career options for physiologists, and will feature prominently on the careers section of the new website.

Education and Outreach committee

With the new Society Strategy aimed at engaging with 16-25 year-olds, most of the discussions at the Education and Outreach Committee meeting in October either focused on exploring new initiatives or reviewing existing activities to achieve this aim. The existing Public Engagement Grant scheme has been reviewed and renamed as the Outreach Grant Scheme, which will prioritise activities engaging with 16-25 year-olds. Applicants will be able to apply for funding to support a broader range of activities that support The Society's vision to see physiology flourish. This scheme will open for applications in December 2018.

The Committee also discussed a new project to conduct some research exploring current education choices and career pathways of 16-25 year-olds. The Committee was presented with an updated version of the "Understanding Life" booklet, which showcases new areas of physiology research along with related career profiles.* It is hoped that the proposed careers project will build on this resource to inform The Society's future careers information, advice and guidance for 16-25 year-olds. The first phase of this work will take place in 2019.

The Committee also reviewed the Research Grants and Techniques Workshops to ensure that they align with the new strategic focus on 16-25 year-olds while still supporting more established researchers. And finally, the Committee agreed to support an Education and Teaching-themed workshop in 2019, on educational research approaches. This workshop will be open to academics, technicians and undergraduates across the life sciences.

*For hard copies of the booklet, please email **education@physoc.org**

History and Archives committee

The History and Archives Committee meeting in October included an update on the upcoming symposium, "Physiology and medicine: First World War perspectives". The Committee discussed chairs and titles for the talks as well as how best to promote the symposium. The WW1 symposium took place in Leeds on 16 November 2018, to coincide with the centenary of the end of WW1, and focused on physiological and medical developments that occurred during the war.

The Committee also discussed the new post of History and Archives Manager who will join The Society in December 2018, to work specifically on History and Archives projects. This will include building a list of Honorary Members past and present. The Committee also provided feedback on The Society's new website and reviewed the Paton Prize Bursary, which offers researchers at any stage of their career £1,000 to carry out a project on the history of the major ideas that have shaped modern physiology and the scientists behind this work. Further details of the Bursary will be published on the website and in a future edition of *Physiology News*.

Meetings committee

The Meetings Committee selected the 18 symposia and a number of satellite meetings for Physiology 2019 in Aberdeen, to ensure a diverse and vibrant scientific programme for the Main Meeting. It also chose the awardee of the Sharpey-Schafer Prize Lecture, which will also be given there.

The Committee reflected on The Society's Themes, recommending some changes to ensure that they represent not only physiology as a subject but also Members' interests. The proposed changes will be reported to Council in December. Two new Theme Leads for Neuroscience were selected.

Finally, verbal reports were received on recent meetings, including Experimental Models in Physiology, From lab to clinic: Pathways to translational brain–machine interfaces for rehabilitation, and Europhysiology 2018.

SPACE

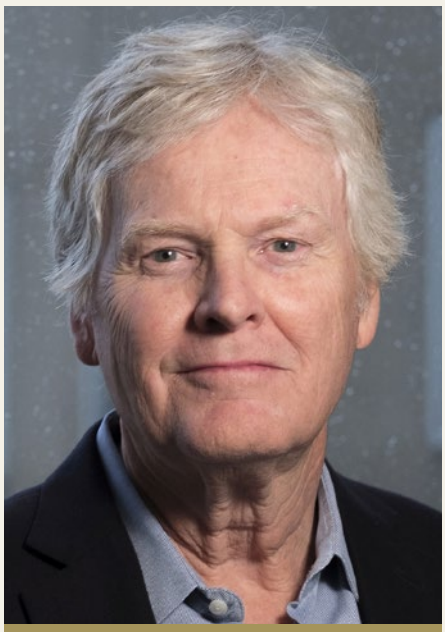
The final frontier

Physiology is out of this world!

The UK Space Agency has awarded more than £3 million to UK researchers to support the exploration of life on Mars and examine the polar regions of the Moon. Congratulations go to the University of Liverpool and in particular to the researchers at Institute of Ageing and Chronic Disease who will be sending laboratory-grown muscle cells into space to investigate skeletal muscle ageing in microgravity. This is very timely as The Society is publishing a Space Special Issue of *Physiology News* next year after our conference Extreme Environmental Physiology: Life at the Limits at the University of Portsmouth in September 2019.

Congratulations to The Society's 2018 Honorary Members

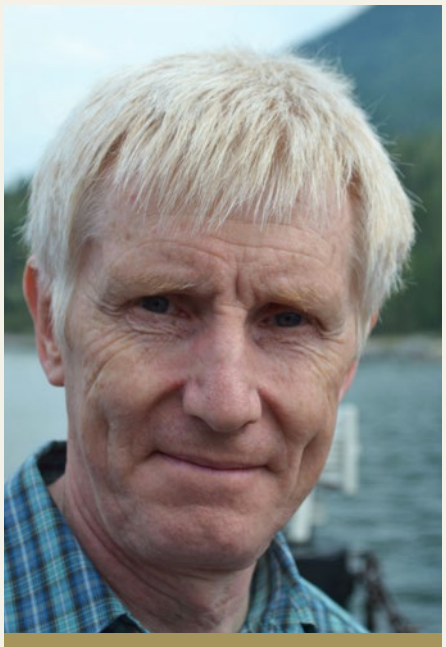
Following their formal announcement at the 2018 Annual General Meeting, Council is delighted to congratulate the 2018 Honorary Members of The Society.



Michael W Young

Michael W Young was awarded Honorary Membership in recognition of the physiological importance of his work on the molecular mechanisms responsible for circadian rhythms, for which he was joint recipient of the 2017 Nobel Prize in Physiology or Medicine, along with Jeffrey C Hall and Michael Rosbash. He is Richard and Jeanne Fisher Professor and Head of the Laboratory of Genetics at The Rockefeller University. He is also the University's Vice-President for Academic Affairs. Young received a BA in biology in 1971 and a PhD in genetics in 1975, both from The University of Texas, Austin. Young is a member of the National Academy of Sciences and a Fellow of the American Academy of Microbiology. In addition to the 2017 Nobel Prize in Physiology or Medicine, he (along with colleagues Jeffrey Hall and Michael Rosbash), received the 2009 Gruber Neuroscience Prize, 2011 Horwitz Prize, 2012 Canada Gairdner International Award, 2012 Massry Prize, 2013 Wiley Prize, and the 2013 Shaw Prize for discoveries of molecular mechanisms that control circadian (daily) rhythms.

Graham Burton was awarded Honorary Membership primarily in recognition for his work on placental physiology in which he has a long-standing interest. Having qualified in medicine from the Universities of Cambridge and Oxford, and pursued research at Cambridge, he now holds the Mary Marshall and Arthur Walton Professorship of the Physiology of Reproduction at Cambridge. One of his most important findings is that the human embryo in the uterus is supported by nutrition from the endometrial glands during the period of organogenesis, prior to onset of the maternal arterial circulation to the placenta at the end of the first trimester. He has published his research findings in *The Journal of Physiology*, organised symposia at Society meetings, mentored numerous young researchers and had a keen involvement in outreach activities designed to increase public awareness of the importance of research in reproductive physiology. He is the inaugural Director of the Centre for Trophoblast Research at the University of Cambridge and was elected a Fellow of the Academy of Medical Sciences in 2011.



Graham Burton

More information on our 2018 Honorary Members can be found on The Society website: **bit.ly/honmemb**

Meeting Notes

Europhysiology 2018

14-16 September 2018,
QEII Centre, London, UK

europhysiology2018.org

Denis Wakeham

Cardiff School of Sport and Health Sciences, UK

Joana Rodrigues & Roxanne Newman

Anglia Ruskin University, UK

Michael Vaughan

University College Cork, ROI

This past September, London was filled with physiologists, hailing from all over the world. They gathered for the inaugural Europhysiology meeting, hosted by Europe's largest physiology societies. The three days of the main meeting, preceded by a day involving the European Early Career Physiologists Symposium and three concurrent satellite meetings, brought together physiologists with varying specialities and interests.

The conference provided a friendly environment for physiologists from all stages of their career. As Denis Wakeham said, "Each of the research symposia I attended were engaging, well organised and included a mix of established and early-career researchers."

The diversity of career stages made for moments for mentoring. "During the late breaking poster session I had an insightful conversation with Vaughan Macefield, about the study of autonomic neuroscience in humans. Discussing the subtle intricacies of data interpretation with an established researcher is of great help to all us early career scientists," continued Wakeham.

The friendly environment enabled undergraduates to have the confidence to present their work. "A fundamental part of science is the presentation of one's work to fellow scientists. Presenting at Europhysiology provided each of us with the chance to discuss our work and gain critical feedback from the experts in an exciting but relaxed atmosphere," said Joana Rodrigues and Roxanne Newman, undergraduates at Anglia Ruskin University, UK.

Michael Vaughan, a young PhD trainee at University College Cork chimed in, "I was terrified at the thought of being surrounded by so many "real scientists", but was surprised to arrive at what I could describe as a massive family reunion. While your new-found "relatives" may be world leaders in their fields, pushing the bounds of physiological knowledge, the atmosphere was very much like one big family gathering."

While there were academics of varying seniority, attendees found it useful that there were also people outside academia, such as representatives from the fields of industry and science communication.

The science presented at the conference was up-to-date, groundbreaking, new research. "We truly felt we were glimpsing through the looking glass!", said Rodrigues and Newman, "During Europhysiology there was something to please every physiologist in the room, from "wet lab" work to education & teaching symposia."

Scattered throughout the days were fascinating glimpses into about how reindeer and bears survive the winter, how the eyes may be an access route to the brain's chronobiology, and how Edmund Goodwyn discovered the diving response, laying the groundwork to stop the inappropriate blowing of smoke to cure drowning.

Daniel Martin kept us all enthralled with his recount of Xtreme-Everest's work atop the world, and how it helped those in the intensive care unit (ICU). The multiple seminars on Education & Teaching gave way to brilliant debates on implementation/ adoption of new techniques, games and assessments. Other talks drew attention to important, but less well-known areas of physiology. Professor Maiken Nedergaard gave an outstanding overview of her pioneering work, investigating the glymphatic system, during her plenary lecture. This clearance system cleans the brain of its waste products. She eloquently illustrated the importance of the glymphatic system for maintenance of brain health.

Check out #europhys2018 on Twitter for the full story. We hope to see you in Berlin for Europhysiology 2020!

Meeting Preview

Life Sciences 2019: Post-Translational Modification and Cell Signalling

17-18 March 2019,
East Midlands Conference Centre,
Nottingham, UK

physoc.org/lifesci2019/

Gary Stephens

University of Reading, UK
Member of Life Sciences 2019
Organising Committee

Even after proteins are built via transcription and translation, post-translational modifications (PTMs) can change their function. As this has implications throughout the body – such as neuronal signalling, cardiac function, circadian rhythms and in diseases including cancer and psychiatric disorders - post translational modifications are an expanding area of scientific research. All physiologists looking to innovate their science by networking across disciplines should attend Life Science 2019, brought to you by The Physiological Society, the British Pharmacological Society and the Biochemical Society.

In addition to symposia and plenary lectures, the meeting will have training events and an early career researcher (ECR) networking event. If you're keen to present your research orally, you're in luck, as a good number of submitted abstracts will be elevated to oral presentations, in particular from ECRs.

PTMs increase the diversity of the protein function, primarily by adding functional groups to proteins, but can also involve the modification of regulatory subunits, or degradation of proteins to terminate effects. PTMs include numerous biologically vital processes such as phosphorylation, glycosylation, ubiquitination, SUMOylation, nitrosylation, methylation, acetylation, lipidation and proteolysis. Identifying and understanding PTMs within major body systems including neuronal, cardiovascular and immune systems is critical in the study of normal physiological function and disease treatment.

As a researcher interested in synaptic function, one symposium that has immediate personal appeal is "PTMs in the regulation of neuronal synapses" which will include how PTMs on both sides of the synapse are fundamental to forms of synaptic plasticity. Matt Gold (University College London, UK) will speak on targeting of the calcium/calmodulin-dependent protein phosphatase calcineurin in postsynaptic spines. Moitrayee Bhattacharyya (University of California, Berkeley, USA) will present about the postsynapse, specifically the role of calcium/calmodulin-dependent protein kinase II in driving synaptic long-term potentiation via modifications in postsynaptic spines. For the ion channel aficionados, Annette Dolphin (University College London, UK) will discuss the role of post-translational proteolytic cleavage of $\alpha 2\delta$ voltage-gated calcium channel subunits in synaptic function.

Protein methylation in health and disease will feature a presentation from Steven Clarke, (University of California, Los Angeles, USA) on crosstalk between methyltransferases to affect the final degree of protein modification and epigenetic control. Kusum Kharbanda (University of Nebraska, USA) will present about how external stimuli such as the consumption of alcohol have important cellular consequences for methyltransferase activity and the development of disease. Pedro Beltran-Alvarez (University of Hull, UK) will detail the combination of biochemical, cell biology, bioinformatics and proteomics methods used to identify the arginine methylome in tissues including platelets and the heart. This has clear functional importance in physiological cardiovascular function.

We hope to see you in Nottingham!

Submit your abstract by 21 January 2019

David Merrett, CC BY 2.0

Meeting Preview

Physiology 2019

8-10 July 2019,
Aberdeen Exhibition and Conference Centre, Aberdeen, UK

physoc.org/physiology2019

Guy Bewick, Derek Ball & Derek Scott

University of Aberdeen, UK
Members of local organising committee

For our Annual Conference next year, you will enjoy a world-class event in Aberdeen, a city with a long heritage of physiology research and education, which is near beaches, whisky trails and wildlife, and experiences 18 hours of daylight in July.

Founded in 1496, the University of Aberdeen has magnificent medieval buildings at the King's College campus. Its scientific pedigree includes five Nobel Prizes, in medicine or physiology, chemistry, physics and peace. Our key physiologist was JJR MacCleod (Nobel Prize, 1923), whose isolation of insulin with Frederick Banting, enabled its use in the treatment of diabetes. Michael Kosterlitz (Nobel Prize, 2016) the son of the remarkable Hans Kosterlitz who discovered the enkephalin pain regulatory system, was also born here. Our current physiological research strengths are in neuroscience, diabetes, nutrition, pharmacology, education and sports science, and we offer world-class sporting facilities.

In the late 1800s, the Universities of Aberdeen, Edinburgh and Glasgow collectively pioneered the teaching of physiology as a distinct discipline in the UK. The strong teaching tradition has continued, as Mary Cotter received The Society's inaugural Otto Hutter Teaching Prize in 2010. Aberdeen's first Regius Professor (William Stirling) joined the foundling Society in 1877, and Aberdeen now has the only such chair in the UK, with the present incumbent being Colin McCaig. Finally, physiology and neuroscience are the two largest cognate degree programmes in the School of Medicine, Medical Sciences & Nutrition, training approximately 50 graduates annually. Across the city, Robert Gordon University's striking Garthdee Campus also delivers substantial physiology teaching components to their health sciences degrees (Nursing, Midwifery and Physiotherapy).

Physiology and teaching aside, Aberdeen boasts beautiful scenery, and is easily accessible by flight or train. Shelter from the Grampian Mountains ensures July precipitation is amongst the lowest for British cities. There are cafes, restaurants and bars to suit all budgets. Aberdeenshire has air and water that are fresh and clean, and miles of sandy beaches, cliffs and mountains. The uncluttered roads give ready access inland to the native wildlife, including red kites, ospreys, buzzards, deer and red squirrels, while our beaches offer views of seals and dolphins. There are over 100 castles (e.g. Craigievar, reputedly inspiring the Disney emblem), countless stone circles, Pictish standing stones, whisky distilleries (seven within a few miles of Aberdeen, and many more beyond), plus golf courses in almost every village. Come and enjoy a warm welcome, long days of great science, and hospitality second to none.

Aberdeen: The scenic, historic, and accessible setting of our Annual Conference, Physiology 2019

Extreme Environmental Physiology: Life at the Limits

Explore how our physiology allows us to visit other worlds, climb the highest mountains and swim in Arctic waters

---

Save the date! 2-4 September 2019

The Physiological Society

Extreme Physiology: Life at the Limits
2-4 September 2019
Portland Building, University of Portsmouth

The Journal of Physiology

SIRT1 overexpression attenuates offspring metabolic and liver disorders as a result of maternal high-fat feeding

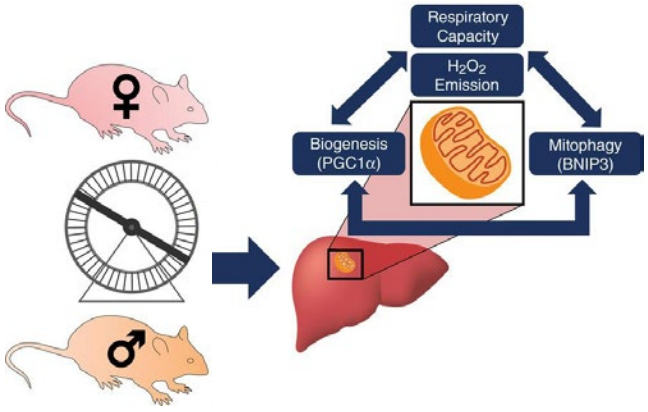
Nguyen LT et al. (31 October 2018).
DOI: 10.1113/JP276957

This study demonstrates that maternal overexpression of Sirtuin 1 (SIRT1), a histone deacetylase ameliorates metabolic disorders present in the offspring of dams fed a high-fat diet. Offspring of mice fed a high-fat diet were glucose intolerant, hyperinsulinaemic and exhibited a reduction in the activity and expression of key enzymes governing insulin signalling. Overexpression of SIRT1 reduced body weight and fat mass and reversed these deleterious effects in addition to preventing hepatic lipotoxicity, inflammation and oxidative stress.

Hepatic mitochondrial adaptations to physical activity: impact of sexual dimorphism, PGC1α and BNIP3-mediated mitophagy

Schulze A et al. (28 August 2018).
DOI: 10.1113/JP276539

This interesting work shows that the liver specific knockout of a key regulator of mitochondrial biogenesis (PGC1α) and mitophagy (BNIP) regulate the hepatic alterations seen in response to physical activity in a sex specific manner. Mice lacking hepatic BNIP3 had elevated levels of electron transport chain (ETC) system enzymes and citrate synthase activity whilst female mice had higher ETC enzymes than males. Similarly, female mice had a higher maximal mitochondrial respiratory capacity (basal, state 3 and state 3s) with palmitoyl carnitine compared to males in addition to reduced hydrogen peroxide production likely due to an improved mitochondrial coupling efficiency.



Illustrated representation of experimental purpose and design.

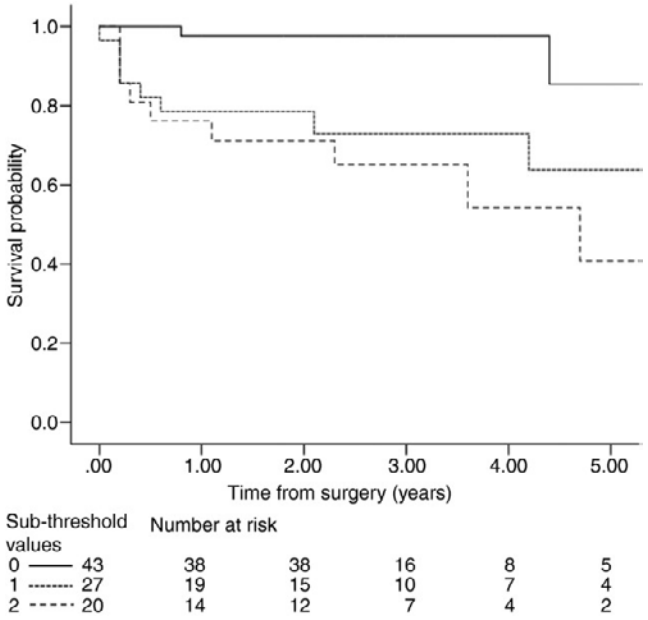
This study examined the effects of increased physical activity through voluntary wheel running (VWR) on mitochondrial adaptations in male and female wild-type (WT) mice, as well as mice with targeted deficiencies in liver-specific PGC1α (LPGC1α+/–) and BNIP3-mediated mitophagy (BNIP3–/–).

Experimental Physiology

Cardiorespiratory fitness is impaired and predicts mid-term postoperative survival in patients with abdominal aortic aneurysm disease

Rose GA et al. 103(11), 1505-1512 (31 October 2018).
DOI: 10.1113/EP087092

The treatment of choice for large abdominal aortic aneurysms (AAA) is currently surgery, but comprises a substantial physiological insult to the patients during the perioperative period, and preoperative risk stratification by cardiopulmonary exercise testing may be a valid tool for optimising perioperative care. In the present study, it was found that AAA patients in which preoperative peak oxygen uptake was less than 13.1 ml O_2 kg^{-1} min^{-1} and where the ventilatory equivalent for carbon dioxide at anaerobic threshold was less than 34 ml O2 kg-1 min-1 were at a markedly increased risk of postoperative mortality.



Kaplan–Meier plot for survival after abdominal aortic aneurysm surgery stratified by the number of subthreshold cardiopulmonary exercise testing (CPET) values.

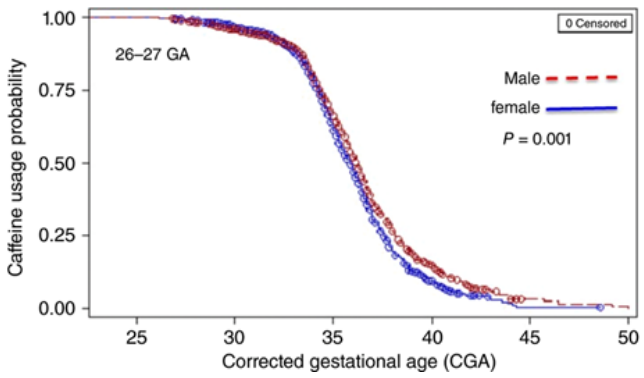
P = 0.01, log-rank test. Subthreshold CPET values: Peak oxygen uptake less than 13.1 ml O_2 kg^{-1} min^{-1} and ventilatory equivalent for carbon dioxide at anaerobic threshold less than 34.

Sex-based differences in apnoea of prematurity: A retrospective cohort study

Bairam A et al. 103(10), 1403-1411 (1 October 2018).
DOI: 10.1113/EP086996

Male sex is a risk factor for respiratory disorders and a poorer outcome after preterm birth, and the present study therefore examined the impact of sex differences on apnoea of prematurity (AOP), which may contribute several complications of prematurity. The records of 24,387 premature infants were reviewed, and showed that infants that developed AOP were born at lower

gestational ages and developed various complications of prematurity more frequently than infants without AOP. Furthermore, the resolution of AOP which took longer in male than in female infants may reflect slower development of respiratory control in males.

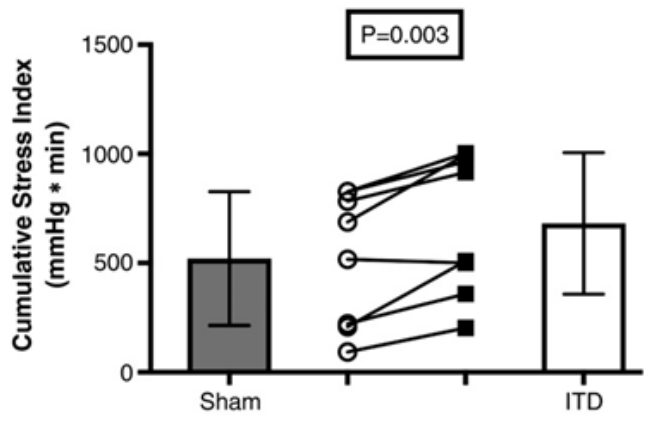


Kaplan–Meier curves showing the probability of caffeine usage in males and females by corrected gestational age (CGA) in infants born between 26 and 27 weeks of gestational age (GA).

Tolerance to a haemorrhagic challenge during heat stress is improved with inspiratory resistance breathing

Huang M et al. 103(9), 1243-1250 (31 August 2018).
DOI: 10.1113/EP087102

Major trauma is the leading cause of death on the battlefield, and the impact of haemorrhage in this context is compounded by concurrent heat stress. In this paper, heat stress was imposed passively using a tube-lined water-perfusion suit, while haemorrhage was concurrently simulated by lower body negative pressure in eight healthy volunteers. Compared to normal breathing, inspiratory resistance breathing by use of an impedance threshold device increased the tolerance to simulated haemorrhage. These findings thus highlight this manoeuvre as a potentially life-saving resuscitative countermeasure in the context of battlefield injuries in hot environments, such as desert climates.



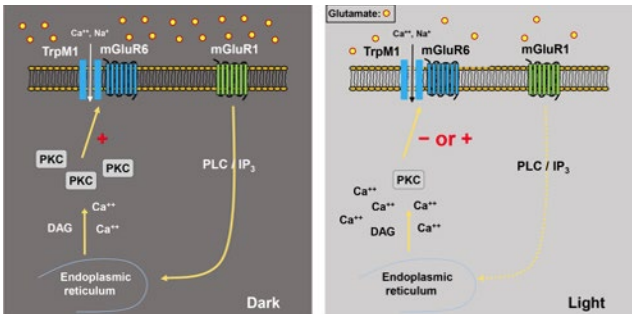
Cumulative stress index to a graded lower-body negative pressure test during normal breathing (Sham) and during inspiratory resistance breathing using an impedance threshold device (ITD). Data are presented as group mean (±SD) and individual data.

Physiological Reports

A group 1 metabotropic glutamate receptor controls synaptic gain between rods and rod bipolar cells in the mouse retina

Hellmer CB et al. 6(20), e13885 (18 October 2018).
DOI: 10.14814/phy2.13885

The rod and cone pathways both contribute to vision in mid-range (mesopic) light conditions. In order to accommodate the transmission of visual information over a wide range of light intensities, control mechanisms in the retina facilitate the amplification or suppression of signals from rods in low and bright light respectively. This paper describes a control mechanism at the rod-rod bipolar cell synapse in which mGluR1 receptor activation, and subsequent PLC-PKCalpha pathway activation, potentiates bipolar cell responses in dim light, but not in bright light.



Schematic models of mGluR1 modulation of the mGluR6-TrpM1 complex. (Dark) mGluR1-mediated signalling activates the phospholipase C-IP3-protein kinase C pathway to amplify mGluR6-evoked responses in the dark. (Light) Elevated intracellular Ca^{2+} blocks or reverses the effect of mGluR1 signalling on mGluR6-mediated responses.

Three weeks of respiratory muscle endurance training improves the O_2 cost of walking and exercise tolerance in obese adolescents

Alemayehu HK et al. 6(20), e13888 (22 October 2018).
DOI: 10.14814/phy2.13888

Obese individuals have low exercise tolerance due, at least in part, to an increased O_2 cost of breathing, resulting in an increased cost of exercise. Respiratory muscle endurance training in a 3 week programme, reduced the O_2 cost of moderate and heavy exercise in obese teenagers and improved exercise tolerance. This suggests that respiratory muscle endurance training could be useful in weight reduction regimens.

A chronology of chronobiology

From plants in cupboards and bovine pineal "popcorn" to mood disorder and cancer therapy

Thomas C Erren

Institute and Policlinic for Occupational Medicine, Environmental Medicine and Prevention Research, University Hospital of Cologne, Germany

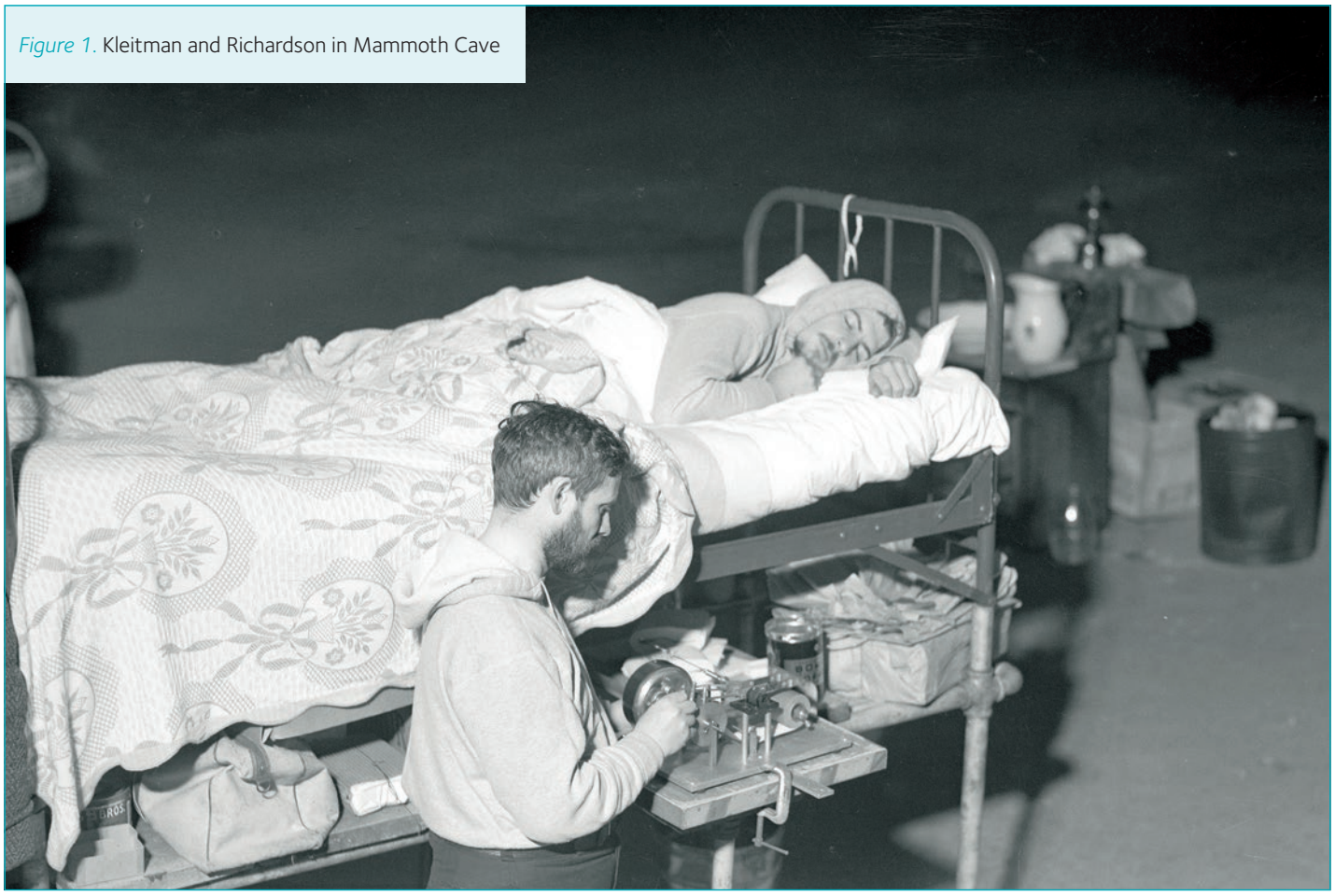
Life on Earth evolved under cyclic light-dark conditions due to our planet's rotation. Circadian physiology, facilitating interplays between light and time and life, allowed species to anticipate daily environmental changes and align their internal time accordingly for competitive edges in survival and evolution. The causal web connecting environmental and circadian times includes complex interactions between: (1) light; (2) our eyes as dual sense organs; (3) the suprachiasmatic nuclei (SCN) – or master clock – in the anterior hypothalamus; (4) peripheral clocks; and (5) melatonin molecules secreted from the pineal gland in response to environmental time cues. Clockwork facets discovered over some 300 years shed light on the evolutionary history of species on Earth, including humans. Importantly, research into determinants and effects of the temporal organisation of physiology can offer fascinating insights into this timing network with possible high relevance for individual and public health.

Indeed, we all have an internal timing system that organises our physiology over time in alignment with periodic zeitgebers (from German, "time-giver") such as the light-dark cycle. For young(er) readers, what challenges or perspectives may derive from grappling with the concept of internal time? First, familiarise yourself with roots of chronobiological thinking. Pause here: consideration of an evolutionary legacy of internal time and circadian organisation across species, including humans, must stimulate further thoughts on integrated circadian physiology. Second, begin to answer how – at an evolutionary scale – abrupt changes such as making the night into day by widely available man-made light since the late 19th century may disrupt ancient health-promoting systems. Third, understanding and possibly clarifying terminology can be an excellent start for chronobiological considerations such as how health may be affected by conflicts between internal time and, for instance, work at chronobiologically unanticipated times.

1720s – 1930s: The foundation of the field

To begin, four key studies can be noted as providing the platform for significant advancements in the field. First and foremost, de Mairan's observation regarding the *Mimosa pudica* plant marks the dawn of chronobiology in 1729. Until his "experiment in a cupboard", the assumption was that the plant opened in the day due to sunlight and closed at night due to darkness. Yet, when de Mairan exposed the plant to total darkness, opening and closing of the flowers continued.

Figure 1. Kleitman and Richardson in Mammoth Cave



His discovery was that an intrinsic timekeeper must be present which is responsive to both light/dark and non-light/dark influences. From here, it took more than 200 years before Kleitman and Richardson entered Mammoth Cave, a location devoid of natural light, to investigate intrinsic timekeepers in humans (Fig. 1). Assuming no environmental time cues, they attempted to switch to a 28-hour sleep-wake cycle. Despite lasting 32 days in the cave, their results of n=2 were inconclusive. Nonetheless, this early attempt to determine whether humans have endogenous clocks, was pioneering for the field. In addition, two decades (1917) before the Mammoth Cave expedition, one peculiar observation prepared the ground for identifying melatonin – now considered one of the body's key time messengers. Namely, when McCord and Allen fed bovine pineal gland materials to *Rana pipiens* tadpoles, a dose-dependent skin lightening occurred and larger viscera could be seen. When investigating vitiligo-like disruptions in skin pigmentation in the 1950s, Lerner *et al.* followed up on these observations to discover that a pineal indole (melatonin) caused melanin granules in frog melanocytes to aggregate and their skin to lighten.

1950s – 2000s: Terminological support for the field

Unambiguous terminology to describe falsifiable concepts is a *conditio sine qua non* for interpretable research. In the 1950s, there was a surge in chronobiological research, and terminology was crucial. In 1951, the German chronobiologist Aschoff termed external or environmental time cues "zeitgeber". These environmental factors were named "synchronisers" by Halberg *et al.* and "entraining agents" by Pittendrigh and Bruce but the three terms are synonymous. In 1958, Lerner *et al.* called the pineal gland factor "melatonin" after showing it inhibited melanocyte-stimulating hormone (MSH) and lightened skin colour in frogs. In 1959, Halberg, after discussion with McDonald (and others) of the Department of Classics at the University of Minnesota, proposed the term "circadian" – deriving from Latin: "circa" (about) and "dies" (day). In 1974, Ehret coined "chronotype" as the temporal phenotype of an organism which captures a biological trait regarding when individuals tend to be awake or asleep. While "circadian disruption" is not clearly defined, "chronodisruption" as the split physiological nexus of internal [circadian clock] and external times was proposed in 2003. Already in 1959, Halberg emphasised what is still true today: "One of the difficulties in correlating the various views and opinions on how periodic biological phenomena are established and maintained lies in the confusion of terms used" (Halberg *et al.,* 1959). In this regard, the 1960 Cold Spring Harbor Symposium: Biological Clocks, Vol. XXV, proved a landmark event, bringing together nestors of chronobiology, laying down "laws" for future investigations, and providing stimulating seeds and feeds for the nascent field.

1950s – 2000s: Nobel-worthy discoveries

Paved by the earlier work, the 1950s brought about a surge in chronobiological research. The selection for this section starts with Axelrod, the 1970 Nobel laureate who completed his PhD at the "early age" of 43. Part of the work which won him the Nobel, viz "Noradrenaline: fate and control of its biosynthesis", involved investigating the pineal gland which produces the bulk of melatonin that enters the blood. Axelrod clarified relationships between melatonin, tryptophan, and serotonin, which all follow circadian rhythm. The isolation of melatonin is a discovery saga of its own. It took Lerner *et al.* no less than 250,000 bovine pineal glands (Fig. 2 - looks like a giant bag of popcorn!) to ultimately characterise the "Dracula molecule" or "chemical expression of darkness". Today we know that melatonin rhythms serve both as a clock and calendar (Reiter, 1993). In the 1960s, Aschoff *et al.* followed up the landmark experiment by Kleitman and Richardson with observation of humans in underground bunkers. Ultimately, it was concluded that human volunteers had endogenously generated circadian sleep-wake cycles.

"Rather than treating physiology and pathophysiology as constants … chronobiology suggests that circadian organisation varies over time and across individuals"

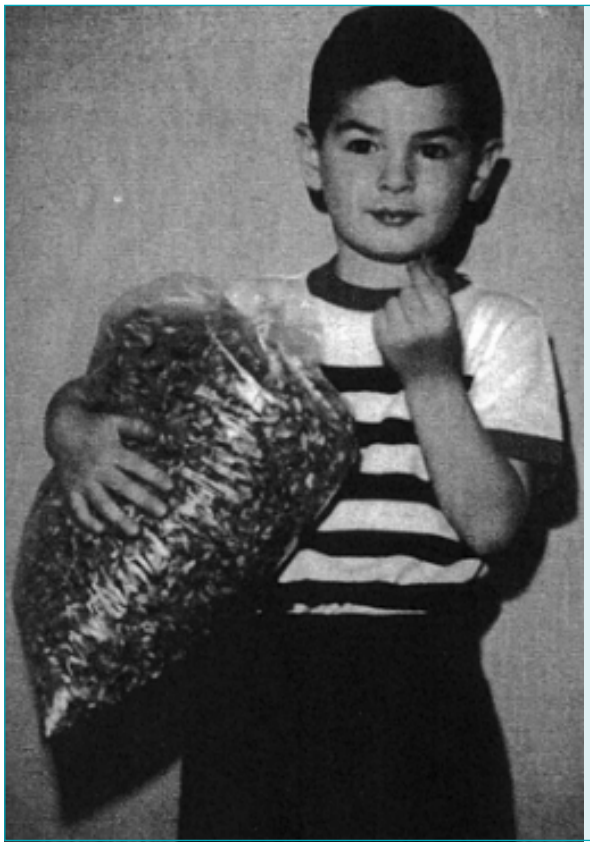


Figure 2. "A four-year-old boy has no difficulty holding a bag with a few thousand lyophilised pineal glands. In his other hand he is holding one gland. It looks like a single piece of puffed wheat or puffed rice. By the time the project was completed, Armour (Laboratories in Chicago) had sent us more than 250,000 frozen glands and we were still complaining that we needed more" (Lerner AB [1999]. Melatonin - without the hype. *Advances in Experimental Medicine and Biology* **460**, 1-3).

One new era for research into chronobiology came with the discovery of first clock mutants in *Drosophila melanogaster* (fruit fly) in 1971 and in *Mesocricetus auratus* (Syrian or golden hamster) in 1988, two examples of (if you will) "natural experiments" which were profitably exploited (Konopka & Benzer, 1971; Ralph & Menaker, 1988). The former led to work which won Hall, Rosbash and Young last year's Nobel award for discoveries of molecular mechanisms controlling the circadian rhythm. Regarding the latter, transplantation of tau mutant SCN into SCN-ablated wild-type animals inflicted the donor's rhythm on the host; namely, they gained the homozygous mutant's 20 hours sleep-wake cycle instead of wild-type 24 hours. This confirmed the SCN (Fig. 3) as the site of the master circadian pacemaker (Ralph *et al.*, 1990).

A new era for photoreception research arrived with understanding that the eye is a dual sense organ. In 1991, circadian responses to light were observed in mice with hereditary retinal disorders despite loss of image-forming visual photoreceptors by Foster *et al.* Vertebrate ancient (VA) opsin discovery in salmon was an intermediate step to ultimately demonstrate that intrinsically photosensitive retinal ganglion cells (ipRGCs) contain the photopigment melanopsin and contribute critically to circadian (non-image-forming) vision (Soni *et al.*, 1998). In 2007, non-rod, non-cone photoreceptors were demonstrated in two humans with rare eye diseases. They had no rods or cones but intact ipRGCs and photoentrainment proved possible (Zaidi *et al.*, 2007). Hattar *et al.* (2002, 2006) illustrated "hardware" connections of ipRGCS to the SCN and further architecture and projections throughout the brain. These await linkage to functional questions: How is circadian time relayed throughout the body? How are health and disease linked with circadian organisation? How can we translate chronobiological insights to combat disease?

Suffice to say, there are numerous discoveries which did not make the cut for this article. For those interested in more, the 1960 Cold Spring Harbor Symposium is an excellent place to start.

1980s-present: Time for translation

First answers to the latter question were provided by Rosenthal *et al.*, (1984). The sleep researchers proposed seasonal affective disorder (SAD) as a syndrome occurring at regular times of the year. On the basis of 29 patients, they concluded that most SAD individuals had a bipolar affective disorder, appeared responsive to changes in latitude-associated photoperiod, and exhibited impaired sleep. Preliminary exploration of how bright light could have antidepressant effects was the prelude to further developments in light therapy.

Another example of translating chronobiological insights into clinical practice is that the value, efficacy, and safety of pharmacological treatments should be tailored to individual internal time. Rather than treating physiology and pathophysiology as constants where one medication timing fits all patients' circadian times, chronobiology

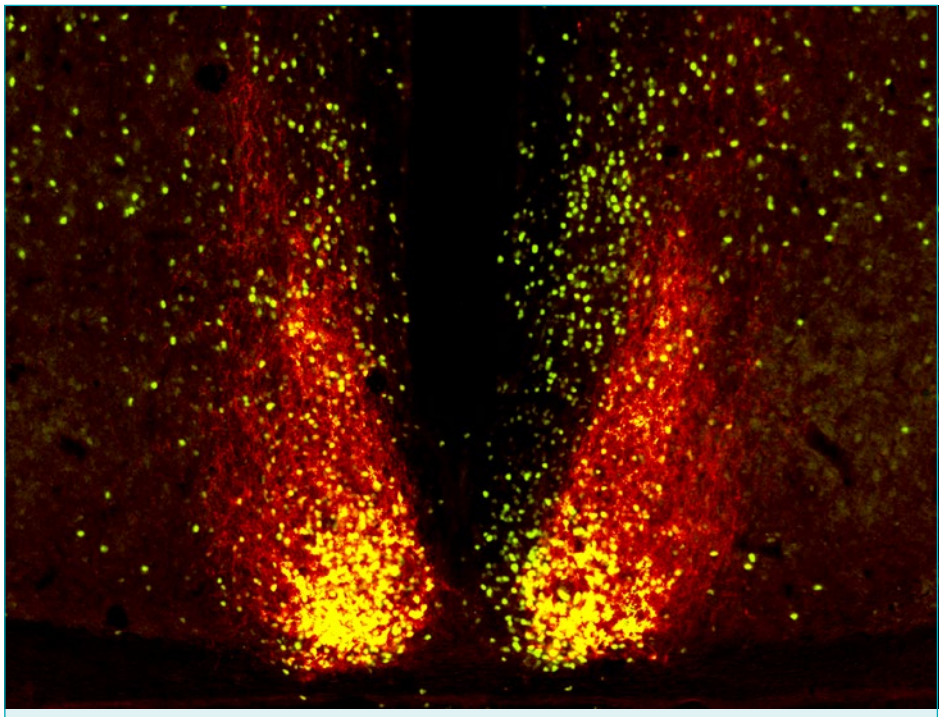


Figure 3. Image of the suprchiasmatic nuclei with cell bodies in yellow and fibres in red - courtesy of the Sleep & Circadian Neuroscience Institute, University of Oxford.

suggests that circadian organisation varies over time and across individuals. Applying this to disease, Lévi and colleagues have been exploring how cancer treatments can be improved by considering circadian timing (Martineau-Pivoteau *et al.,* 1996).

Future challenges and perspectives

Studying effects of man-made light pollution on health and disease in organisms, including humans, is a future challenge. For instance, in 2007, the International Agency for Research on Cancer concluded that shift-work involving circadian disruption is a probable human carcinogen (Group 2A). A major problem, however, is that the key link in the plausible chain of cancer causation, viz circadian disruption, has neither been defined nor were suggestions made on how to assess doses of circadian disruption. Various metrics to allow computation of chronodisruption or circadian misalignment or sleep deficiency all build upon individuals' discrepant internal and external times due to e.g. shift-work. But there is a big "if" regarding all these metrics; namely, how chronotype or internal time can be appropriately assessed over prolonged periods (months/years) remains unanswered (Erren *et al.,* 2018).

It is also of interest whether individuals vary in their susceptibility to circadian challenges. In this vein, researchers have begun to explore whether Perinatal Light Imprinting of Circadian Clocks and Systems (PLICCS) renders individuals born under winter light conditions or photoperiods more susceptible to circadian challenges later in life than those born under summer light conditions (Lewis & Erren, 2017).

Overall, from a public health point of view, a promising approach to improve circadian-related health and performance may be to strive for zeitgeber hygiene. That is to say, strive to align diverse zeitgebers such as light, food, activities, and social factors such that they interact synergistically rather than antagonistically.

A case in point to fuel readers' curiosity and scientific creativity can be recent observations by Wehr (2018). His report of potential synchronicity of mood cycles in rapid cycling bipolar disorder patients with lunar cycles, if not falsified, could impact how we understand disease causation, diagnosis and prevention and, more generally, chronobiology. If true, bipolar patients might switch rapidly between two rhythmic periods: the circadian period seemingly free-running, viz close to 25 hours, when symptomatic and 24 hours (entrained to natural light-dark cycle) when not. Now, if relevant moon-associated zeitgeber signalling was corroborated, what we call endogenous circadian periods today might be considered a misnomer because what we measured might have been affected by un(der)-appreciated zeitgeber information from the Moon.

In conclusion, careful and open-minded chronobiology-based and chronobiology-targeted research can pave the road to important insights into circadian time, on the one hand, and health and disease, on the other.

References

Erren TC, Groß JV, Lewis P (2018). Computing sleep deficiency. *Journal of Sleep Research* **27**, e12630

Halberg F, Halberg E, Barnum CP *et al.* (1959). Physiologic 24-hour periodicity in human beings and mice, the lighting regimen and daily routine. In Photoperiodism and Related Phenomena in Plants and Animals. *American Association for the Advancement of Science* **55**, 803-878.

Hattar S, Liao HW, Takao M *et al.* (2002). Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* **295**, 1065-1070.

Hattar S, Kumar M, Park A *et al.* (2006). Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *Journal of Comparative Neurology* **497**, 326-349.

Konopka RJ, Benzer S (1971). Clock mutants of *Drosophila melanogaster. Proceedings of the National Academy of the United States of America* **68,** 2112-2116.

Lewis P, Erren TC (2017). Perinatal light imprinting of circadian clocks and systems (PLICCS): The PLICCS and cancer hypothesis. *Frontiers in Oncology* **7,** 44.

Martineau-Pivoteau N, Levi F, Rolhion C *et al.* (1996). Circadian rhythm in toxic effects of cystemustine in mice: relevance for chronomodulated delivery. *International Journal of Cancer* **68,** 669-674.

Ralph MR, Menaker M (1988). A mutation of the circadian system in golden hamsters. *Science* **241,** 1225-1227.

Ralph MR, Foster RG, Davis FC *et al.* (1990). Transplanted suprachiasmatic nucleus determines circadian period. *Science* **247**, 975-978.

Reiter RJ (1993). The melatonin rhythm: both a clock and a calendar. *Experientia.* **49**, 654-664.

Rosenthal NE, Sack DA, Gillin JC *et al.* (1984). Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. *Archives of General Psychiatry* **41,** 72-80.

Soni BG, Philp AR, Foster RG *et al.* (1998). Novel retinal photoreceptors. *Nature* **394,** 27-28.

Wehr TA (2018). Bipolar mood cycles and lunar tidal cycles. *Molecular Psychiatry* **23,** 923-931.

Zaidi FH, Hull JT, Peirson SN *et al.* (2007). Short-wavelength light sensitivity of circadian, pupillary, and visual awareness in humans lacking an outer retina. *Current Biology* **17,** 2122-2128.

What makes a good night's sleep?

The external and internal factors that influence a good night's sleep

Ciro della Monica

Derk-Jan Dijk

Surrey Clinical Research Centre and Surrey Sleep Research Centre, University of Surrey, UK

We all experience good and bad nights of sleep, and we know that if we don't sleep well this profoundly impacts our mood, alertness, productivity, health and well-being. But what is it that defines a good night's sleep and is this the same for everyone? We briefly explore the physiology of sleep and how it is regulated, the aspects of sleep that contribute to sleep quality and brain health, and the factors (internal and external) that put our sleep at risk.

What is sleep and how is it regulated?

The phenomenology of sleep

The definition of sleep as "a reversible behavioural state of perceptual disengagement from, and unresponsiveness to, the environment" (Carskadon & Dement, 2011) captures some of the essential differences between wakefulness and sleep. During wakefulness we actively interact with our environment, and are conscious of our surroundings and ourselves. During sleep this consciousness ceases, except for when we dream.

Moving from wakefulness to sleep and dreaming is associated with changes in brain activity (Fig. 1). During wakefulness brain waves are fast with a low amplitude. When we enter sleep the frequency of brain waves becomes progressively slower and their amplitude increases. This part of sleep is classified into three different stages (N1, N2, and N3), with N3 often considered "deep" sleep and called slow-wave sleep (SWS). The N refers to non-Rapid Eye Movement sleep (NREM), because, unlike in wakefulness, there are no rapid eye movements in this sleep state. After a first episode of NREM we enter Rapid Eye Movement (REM) sleep. The brain activity during this state is somewhat similar to wakefulness and, as the name suggests, there are rapid eye movements even though the eyes are closed. REM sleep is further characterised by muscle atonia, and when we wake up from REM sleep some of us will, for a short period, feel paralysed and often remember our dreams. During a normal night of sleep there will be four to five cycles of NREM-REM sleep, each lasting 90 – 120 min (Fig. 2). The content of the cycles changes as the night progresses. Initially there is much SWS while REM periods are short; later on there will be less and less SWS with REM periods becoming longer. Both NREM and REM sleep are interrupted repeatedly by short periods (half a minute or slightly longer) of wakefulness because, for example, we move or hear a sound. In one night there may be several very short awakenings, very few of which we will remember (e.g. 16 objective vs. 2 subjective median awakenings, della Monica *et al.*, 2018). Brain activity, muscle tone, and eye movements are not the only variables that change across wakefulness, NREM, and REM sleep. Heart rate, hormones, body and brain temperature are all affected and exhibit predictable changes.

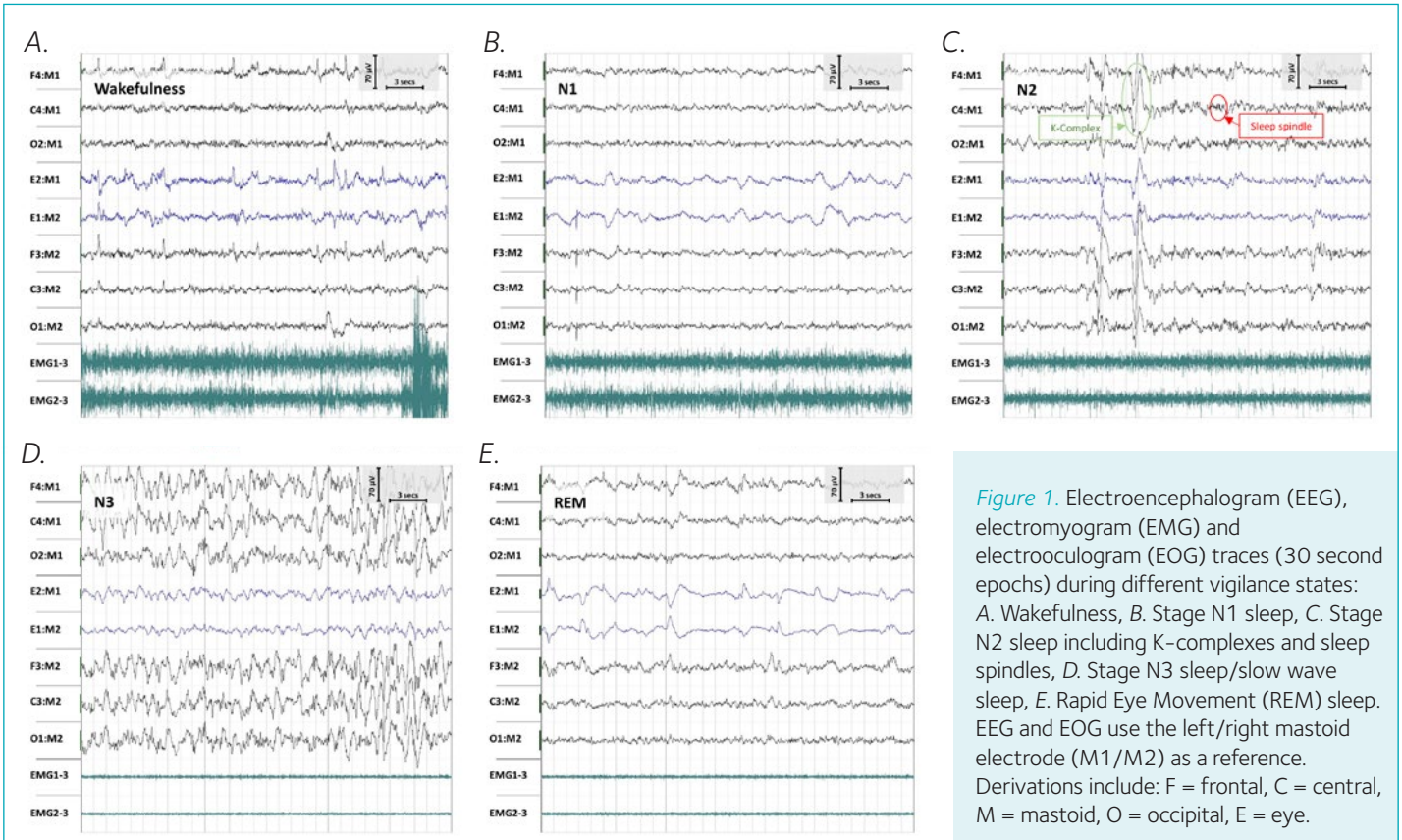


Figure 1. Electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) traces (30 second epochs) during different vigilance states: *A.* Wakefulness, *B.* Stage N1 sleep, *C.* Stage N2 sleep including K-complexes and sleep spindles, *D.* Stage N3 sleep/slow wave sleep, *E.* Rapid Eye Movement (REM) sleep. EEG and EOG use the left/right mastoid electrode (M1/M2) as a reference. Derivations include: F = frontal, C = central, M = mastoid, O = occipital, E = eye.

The regulation of sleep

The timing of sleep and the typical phenomenology of a night's sleep are regulated by two processes (Borbély, 1982) (Fig. 3). The first process, referred to as a homeostatic process (Process S), essentially monitors time awake with sleep debt increasing during wakefulness and dissipating during sleep. The progressive reduction in SWS in the course of a night of sleep and the increase in SWS following sleep deprivation is thought to reflect this homeostatic process.

The second process is the circadian process (Process C). The circadian pacemaker located in the hypothalamus drives ~24-hour rhythms in physiology and behaviour including a rhythm in sleep-wake propensity. The circadian drive for wakefulness increases progressively during the day, peaks during the early evening hours and then suddenly subsides at the beginning of the night, at around the time of the onset of secretion of the hormone melatonin. Later in the night, the circadian process actively promotes sleep, particularly REM sleep. Thus, during the day, the wake-dependent increase in homeostatic sleep drive is countered by the progressive increase in the circadian drive for wakefulness. During the night the homeostatic dissipation of sleep propensity is countered by the circadian increase in sleepiness. Under normal conditions, when we work during the day and sleep at night, these two processes combine to produce consolidated episodes of daytime wakefulness and nocturnal sleep (Dijk & Czeisler, 1994). Taking these two processes into account and knowing that the circadian process is rather inert, i.e. cannot be shifted easily, it is easy to understand why shift workers struggle to sleep during the day and to stay awake at night.

Over the years, many experiments have confirmed the predictions of the two-process model and new aspects have been discovered. For example, it has been demonstrated that sleep homeostasis is to some extent regional and use-dependent. Thus, the build-up and dissipation of Process S is fastest in those areas of the brain which have been most active during the day. Furthermore, hypotheses about the neurochemical and neuronal basis of the sleep homeostatic process have been proposed. The "adenosine" hypothesis of sleep regulation states that neuronal activity is associated with the release of adenosine, which then binds to adenosine receptors and makes us sleepy. When we drink coffee to stay awake we make use of this system because caffeine blocks adenosine receptors. The "synaptic homeostasis hypothesis of sleep function" proposes that during wakefulness when we interact with the environment and much information enters our brains, connections between neurons (synapses) become stronger and larger. This cannot go on forever because our brain has limited space. Therefore it is thought that during sleep the overall synaptic strength is rebalanced (Tononi & Cirelli, 2014).

Genetic variation in the generation of circadian rhythms and in the speed of our clocks have also been identified (Zhang *et al.*, 2011). If your genetic makeup makes your circadian clock tick fast you will be a morning type (i.e. "early bird"), whereas a genetically slow ticking clock will make you an evening type (i.e. "night owl"). However, you cannot blame everything on your genetic circadian make-up. Behavioural choices, such as how much artificial light we consume in the evening, have a profound influence on the circadian clock and our ability to get up in the morning (Skeldon *et al.*, 2017).

What does good and bad sleep really mean?

Sleep quality can be assessed both subjectively, through completion of questionnaires ("how well did you sleep?") and objectively, through polysomnography (PSG) i.e. measurement of brain waves, muscle tone, eye movements, blood oxygen levels, movements of limbs etc. during sleep.

Objective vs. subjective quality of sleep

From PSG data, objective parameters such as total sleep time, % time spent in each sleep stage, time to fall asleep (sleep onset latency), sleep efficiency, and number of awakenings during the night can be derived. You can then determine which objective parameter best correlates with the subjective experience of sleep.

"Sleep is regulated by homeostatic and circadian processes that, respectively, monitor sleep need and appropriate sleep timing"

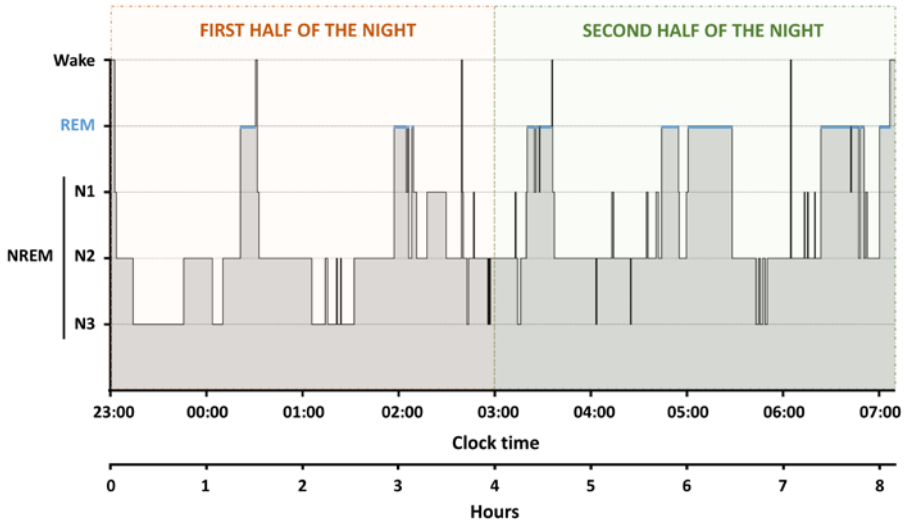


Figure 2. Schematic representation of a typical night of sleep (hypnogram) for a young adult who sleeps 23:00 – 07:00 h, showing the cycles of NREM (non-rapid eye movement) and REM (rapid eye movement) sleep, and the progressive reduction of Stage N3/Slow Wave Sleep and increase in REM sleep across the night.

We assessed the sleep of 206 healthy men and women (20 – 84 years old) without sleep complaints (della Monica *et al.*, 2018). After controlling for the age- and sex-related changes in sleep, we found that while inter-individual variations in SWS (deep sleep) could not predict subjective sleep quality, two other PSG-derived variables could. A large number of night awakenings (NAW) was associated with reports of poor quality sleep. Longer duration of REM sleep correlated with self-reported good sleep quality and how refreshed people felt upon awakening. Interestingly, the associations between objective sleep variables and subjective sleep quality was much stronger in women than men, and was consistent across the whole age range studied.

Another large scale study in 1483 older adults (≥65 years) (Kaplan *et al.*, 2017) also reported that sleep continuity-related measures are an important determinant of subjective sleep quality, although in this study the role of REM sleep was not so clear. However, a recent comparison of patients with primary insomnia and good sleepers found that the patients spent significantly less time in REM (Baglioni *et al.*, 2014) supporting the notion that REM sleep is important for sleep quality.

Objective sleep quality: Association with brain function

We may also want to know which aspects of sleep contribute to objective brain functioning or brain health. There are many aspects to brain function: alertness, mood, attention, working memory, long-term memory, speed of response, creativity, ability to plan ahead, ability to shift from one task to another, etc. These can be assessed by a wide variety of performance tests and questionnaires, and many of these aspects of brain function change with age, some more than others.

To reduce the enormous amount of variables, data reduction approaches such as factor analysis can be used. In one such approach, we assessed 51 performance variables and reduced these to four factors, the most important three of which were: mood/alertness, response time, and accuracy (della Monica *et al.*, 2018). With age we become more alert, and our mood is more positive. Our response times become slower but we maintain accuracy. Assessment of the independent contribution of objective sleep parameters showed that more slow wave sleep predicted faster response times. Fewer awakenings and more REM sleep were associated with maintained accuracy. These observations were made in healthy people without signs of more than normal age-related cognitive decline. Other studies have shown that sleep continuity and REM sleep are protective against more severe cognitive decline and the development of dementia (see della Monica *et al.*, 2018 for references). Sleep disorders, such as sleep disordered breathing, also contribute to cognitive decline. The mechanisms through which normal sleep and sleep disorders contribute to brain function remains unknown. However, some researchers have suggested that sleep contributes to brain health through clearing of toxic or harmful metabolic by-products from the brain.

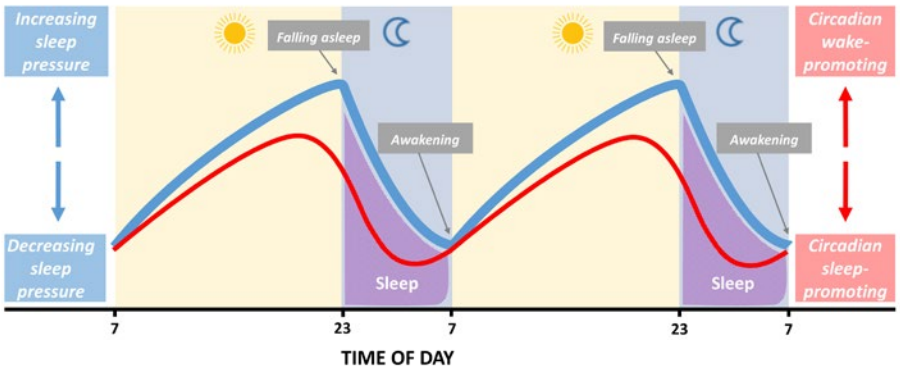


Figure 3. Diagrammatic representation of the regulation of sleep and wake through Process S (sleep pressure represented by blue line) and Process C (circadian system represented by red line).

Which external and internal factors can impact the quality of our sleep/wake cycle?

The bedroom environment can have a profound impact on the quality and quantity of sleep. Noise and low and high temperatures are often cited as reasons for poor sleep. In a survey of 1375 individuals in Switzerland, self-reported sleep quality was linked to annoyance by nocturnal traffic noise (Frei *et al.*, 2014). In a Norwegian survey of 2898 participants, a positive relationship was found between exposure to traffic noise and psychological distress symptoms in those with poor sleep quality, suggesting these individuals may be more vulnerable to the effects of traffic noise (Sygna *et al.*, 2014). An analysis of 765,000 US survey respondents (2002–2011) and nocturnal environmental temperature information demonstrated that increased temperatures at night are associated with elevated self-reports of insufficient sleep particularly in summer and in older individuals (Obradovich *et al.*, 2017). This suggests that climate change may impact sleep, and our hot and noisy cities don't make for a good sleeping environment.

Light is another physical environmental factor that is known to affect sleep. Moonlight and the full moon have been thought to disrupt sleep but recent studies in the laboratory (della Monica *et al.*, 2015) and at home (Haba-Rubio *et al.*, 2015) have failed to support this notion. There are more and more sources of biologically effective artificial light. LEDs and screens from smart phones/tablets emit light which often has a high blue light content. Artificial evening light can slow down our clock making us think that it is not yet time to go to bed. Light has also direct alerting effects; in other words, makes us less sleepy at any time of day. Just like drinking coffee later in the day, consuming too much light in the evening will keep you awake and, alongside frequent texting and internet activities, will make it difficult to switch off.

In fact, not being able to switch off and worries about work and family are among the most commonly cited internal reasons for poor sleep. Maybe this is not surprising, but it nevertheless shows that besides biological processes, such as sleep pressure and circadian rhythmicity, and external environmental factors, there are cognitive or psychological factors that have a profound impact on sleep quality. Importantly, these biological and non-biological factors interact. This is well illustrated by cognitive behavioural therapy for insomnia, of which a central component of this multicomponent therapy is sleep restriction. Limiting sleep increases homeostatic sleep pressure, makes you fall asleep more quickly, and thereby helps the patient to disengage from those internally generated worries.

Conclusion

Recent research confirms the importance of good quality sleep and has identified some of the key aspects of sleep contributing to subjective and objective sleep quality. It has identified factors that may jeopardise a good night's sleep and simple changes to our environment and lifestyle that can be made to improve sleep.

References

Baglioni C, Regen W, Teghen A *et al.* (2014). Sleep changes in the disorder of insomnia: A meta-analysis of polysomnographic studies. *Sleep Medicine Reviews* **18**, 195–213.

Borbély AA (1982). A two process model of sleep regulation. *Human Neurobiology***1**, 195–204.

Carskadon MA, Dement WC (2011). Normal Human Sleep: An Overview, in: *Principles and Practice of Sleep Medicine.* Elsevier Saunders, St. Louis, 16–26.

della Monica C, Atzori G, Dijk D-J (2015). Effects of lunar phase on sleep in men and women in Surrey. *Journal of Sleep Research* **24**, 687–694.

della Monica C, Johnsen S, Atzori G *et al.* (2018). Rapid eye movement sleep, sleep continuity and slow wave sleep as predictors of cognition, mood, and subjective sleep quality in healthy men and women, aged 20–84 years [Online]. *Frontiers in Psychiatry* **9,** 255. DOI: 10.3389/fpsyt.2018.00255

Dijk D-J, Czeisler CA (1994). Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. *Neuroscience Letters* **166**, 63–68.

Frei P, Mohler E, Röösli M (2014). Effect of nocturnal road traffic noise exposure and annoyance on objective and subjective sleep quality. *International Journal of Hygiene and Environmental Health* **217**, 188–195.

Haba-Rubio J, Marques-Vidal P, Tobback N *et al.* (2015). Bad sleep? Don't blame the moon! A population-based study. *Sleep Medicine* **16**, 1321–1326.

Kaplan KA, Hirshman J, Hernandez B *et al.* (2017). When a gold standard isn't so golden: Lack of prediction of subjective sleep quality from sleep polysomnography. *Biological Psychology* **123**, 37–46.

Obradovich N, Migliorini R, Mednick SC *et al.* (2017). Nighttime temperature and human sleep loss in a changing climate [Online]. *Scientific Advances* **3**(5), e1601555. DOI: 10.1126/sciadv.1601555

Skeldon AC, Phillips AJK, Dijk D-J (2017). The effects of self-selected light-dark cycles and social constraints on human sleep and circadian timing: a modeling approach [Online]. *Scientific Reports* **7**, 45158. DOI: 10.1038/srep45158

Sygna K, Aasvang GM, Aamodt G, Oftedal B, Krog NH (2014). Road traffic noise, sleep and mental health. *Environmental Research* **131**, 17–24.

Tononi G, Cirelli C (2014). Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron* **81**, 12–34.

Zhang L, Jones CR, Ptacek LJ, Fu Y-H (2011). The Genetics of the Human Circadian Clock, in: *Advances in Genetics.* 231–247.

A time to fast, a time to feast

The concept of chrononutrition

Henrik Oster

Lichtenberg Endowed Chair of Neurobiology, Institute of Neurobiology, Centre of Brain, Behaviour & Metabolism, University of Lübeck, Germany

In the Bible it is written, "There is a time for everything, and a season for every activity under the heavens" (Book of Ecclesiastes). It goes on listing various timed activities, from being born and dying to war and peace. There is no mention of eating and fasting, though, which is remarkable when considering that (a) many religions pay special attention to dietary rules including its timing, and (b) that both old folk wisdom and recent research data suggest that the timing of meal intakes may have profound effects on well-being and health. The latter is linked to our internal clock system.

Circadian clocks and rhythms

During the course of evolution, most species on this planet have developed internal timing systems in order to track the course of the 24-hour day under noisy environmental conditions. These circadian (from Latin *circa diem* – "around the day") clocks coordinate physiology and behaviour and enable an organism to anticipate daily recurring events and demands. In humans, circadian clocks control daily rhythms in a wide array of biological functions, from sleep-wake behaviour to cognitive processes and immunity.

At the molecular level, circadian clocks are based on transcriptional-translational feedback loops comprising a set of clock genes and their corresponding proteins (Takahashi, 2017). Two transcriptional activators, CLOCK (circadian locomotor output cycles kaput) and BMAL1 (brain and muscle ARNT-like 1/ARNTL) promote transcription of three *PERIOD* (*PER1-3*) and two CRYPTOCHROME (CRY1/2) genes during the day. *PER* and *CRY* proteins form dimers to translocate back into the nucleus during the night, inhibiting CLOCK/BMAL1 activity – thus shutting down their own production (Fig. 1). Towards the end of the night, PER/CRY complexes are degraded, freeing CLOCK/BMAL1 from repression and reinitiating the next circadian cycle. Further feedback loops stabilise this core clock oscillator. Importantly, besides *PER*s and *CRY*s, large numbers of clock-controlled genes show rhythmic regulation of transcription, thereby translating clock-time information into physiological functions. It is estimated that 5-10 % of active genes in each tissue are under circadian control. In mammals, a central circadian pacemaker resides in the hypothalamic suprachiasmatic nucleus (SCN), coordinating clocks in all tissues of the body with each other and with the external light-dark cycle.

Clock disruption and metabolic homeostasis

An important target of the circadian clock is energy metabolism (Bass, 2012). Circadian clocks in central regulatory circuits control appetite and energy expenditure, while clocks in peripheral metabolic tissues modulate all levels of energy conversion – from food digestion and nutrient absorption in the intestinal tract to energy storage as glycogen in liver and muscle and as lipid droplets in

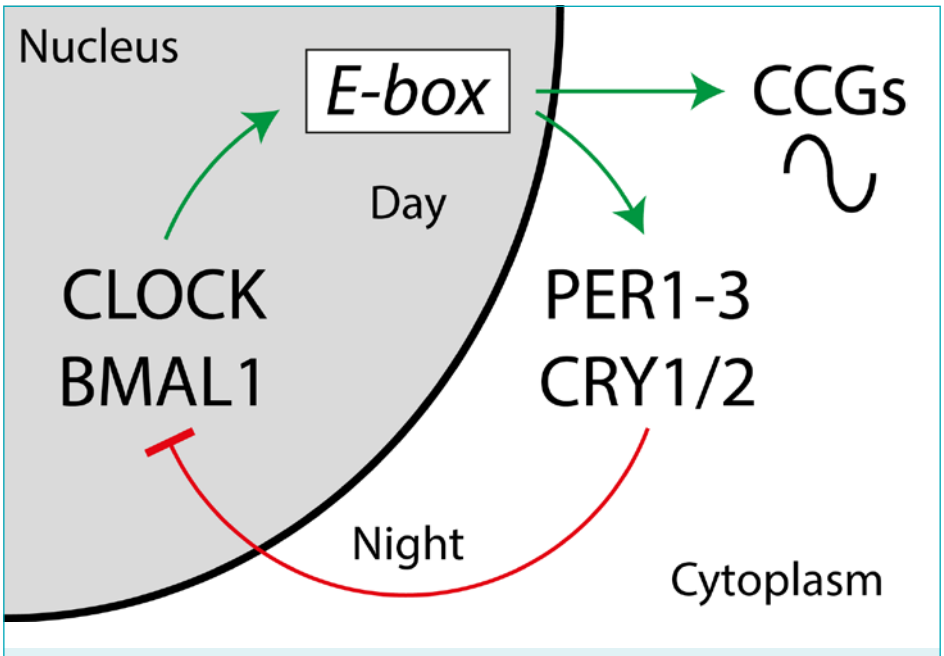


Figure 1. The core transcriptional-translational feedback loop of the mammalian circadian clock. The transcription factors CLOCK and BMAL1 drive expression of *Per* and *Cry* genes via *E-box* enhancer binding during the day. Towards the evening, PER/CRY complexes relocate into the nucleus where they inhibit CLOCK/BMAL1 activity, thus shutting down their own transcriptions. At the same time, CLOCK/BMAL1 regulate tissue-specific clock-controlled genes (CCGs) in a circadian fashion, thus regulating cellular physiology across the 24-hour day.

"In our modern societies of food abundance and 24-hour demands, however, this ancient system frequently reaches its limits"

adipose tissues. Further, systemic regulators of energy metabolism such as insulin and leptin and the autonomic nervous system are regulated by circadian clocks.

This intricate network of circadian checkpoints allows for a tight regulation of metabolic functions along the course of the day, optimising energy efficiency and improving evolutionary fitness under natural conditions (Fig. 2). In our modern societies of food abundance and 24-hour demands, however, this ancient system frequently reaches its limits. More and more people work shift schedules with unnatural sleep and meal conditions, while even non-shift workers disrupt natural timing cues (or *Zeitgeber* – from German "time giver") of their circadian metabolism by artificial lighting or transcontinental air travel. In shift workers, the temporal coordination of physiological processes is altered, rendering them more vulnerable to a whole range of disorders, from obesity to depression and even cancer. Chronodisruptive risk factors for shift workers include nocturnal light exposure (acting through the SCN), mistimed meal intake (acting through peripheral clocks), sleep loss and disruption, and the alteration of endocrine signals such as cortisol and melatonin. In consequence, virtually all major metabolic diseases are more prevalent in shift workers than in non-shift workers. As two examples, the risk for type-2 diabetes is up by more than 50 % in shift workers, for hypertension by about 30 % (Lemmer & Oster, 2018).

Circadian regulation of appetite

Energy homeostasis is defined as the balance between energy intake and expenditure. Already at the level of appetite regulation, circadian clocks play an important role. One principle regulator of food intake is sleep. Quite obviously, during sleep eating is impossible. At the same time, during the circadian rest phase (i.e. the night in humans and the day in nocturnal rodents) appetite is suppressed – with further inhibition during actual sleep. While clocks in hypothalamic nuclei involved in energy balance affect the homeostatic aspects of appetite regulation, central reward pathways have been implicated in food choice and the selection of different nutrient sources. Again, circadian clocks are involved in regulating these hedonic aspects of appetite. This represents a major target for physiologists, pharmacologists, and nutrition scientists considering that in an environment of abundant food availability and constant psychological manipulation by advertisements, hedonic appetite drive may become the determining factor of energy homeostasis and metabolic health. Recent data suggest that dopaminergic reward circuits may be under circadian control. Dysregulation of clocks in these circuits may affect externalised eating behaviour and promote food overconsumption – but also other aspects of addictive behaviours (Blancas-Velazquez *et al.*).

Food as a Zeitgeber

Not only do clocks regulate appetite and food intake, the timing of meals and meal composition may feed back on circadian clock function. Rodent experiments have shown that clock gene activity rhythms in peripheral tissues such as the liver and adipose tissues respond rapidly to changes in the daily feeding schedule. In extreme cases such as rest phase-only eating, this results in an uncoupling of peripheral clocks and rhythms from the SCN pacemaker, leading to a state of internal desynchrony (Landgraf *et al.*, 2017). Factors involved in this uncoupling are insulin and incretin peptides such as glucagon-like peptide 1 (GLP-1) and oxyntomodulin. The nature of nutrients may further affect the circadian system. Under a normal chow diet (ca. 10 % fat), mice eat more than 80 % of their food during the (active) night period. If they are shifted to a high-fat diet (40-60 % fat), they increasingly continue feeding during the day (up to 40 %), resembling feeding behaviour in mice with genetically ablated clock function. In mice and in humans, such rest phase eating has been associated with increased body weight. Thus, high-lipid diets can lead to a vicious cycle – promoting rest-phase eating and disrupting circadian clock rhythms, both of which promote overeating and weight gain. It has been suggested that this phenomenon itself may explain most of the metabolic consequences of shift work, but may also impact on other aspects of obesity such as systemic inflammation or addictive behaviours.

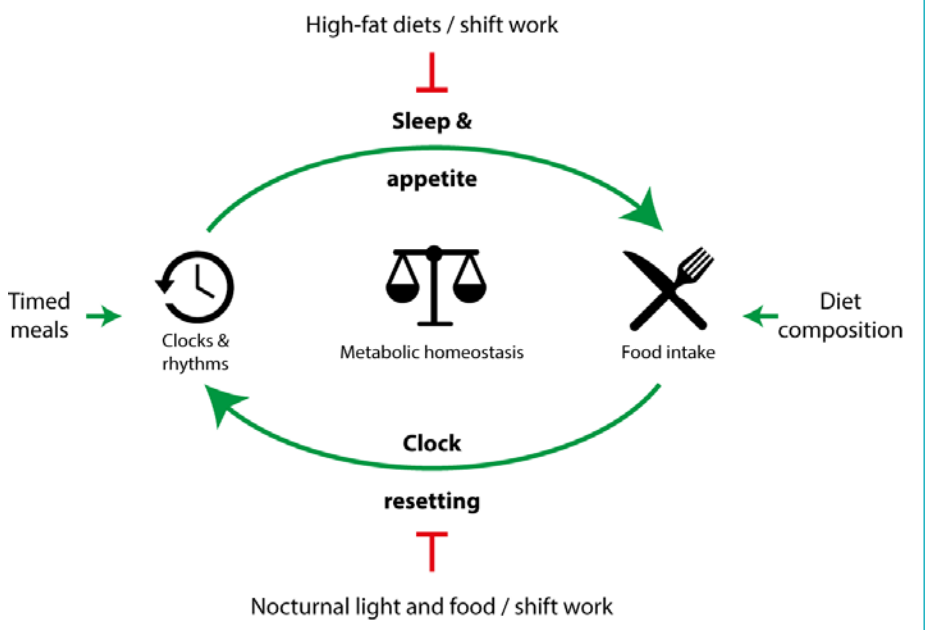


Figure 2. Crosstalk between circadian clocks and energy metabolism. Through the coordination of central and peripheral clocks, circadian rhythms of appetite, food intake, and nutrient metabolisation are regulated. *Vice versa*, the timing and composition of meals may feed back on circadian network regulation. Shift work or the consumption of high-fat diets may disturb this balance by affecting clock network coordination or by directly affecting appetite and activity rhythms. The stabilisation of circadian rhythms - by e.g. timed meal intake or regular sleep-wake schedules - may be a protective factor of metabolic homeostasis.

"A high-fat diet throughout the day leads to a massive increase in body weight… If, however, food is restricted to just 8 h during the active phase, animals stay slim!"

Time-restricted (interval) diets

Considering the profound effect of meal timing on circadian function, researchers like Satchin Panda from the Salk Institute in La Jolla, USA had the idea to turn this around and use meal timing as an intervention to positively affect energy homeostasis and other disorders associated with circadian disruption (Longo & Panda, 2016). In C57BL/6 mice, a high-fat diet provided throughout the day leads to a massive increase in body weight - up to 100 % in just 10 weeks! If, however, access to food is restricted to just 8 hours during the active phase, animals stay slim (about 10 % weight gain) although energy intake is comparable to that of their *ad-libitum* fed mates. Similarly, in humans, long-term monitoring of meal intake patterns revealed that most of us regularly eat during a time window of 18 hours starting at around 6 am. When subjects were asked to reduce this window to 10 hours, they lost around 5 % body weight within 4 months without any calorie restrictions (Gill & Panda, 2015). These data suggest that meal (or rather fasting) timing may be an important regulator of energy homeostasis and that a resetting of the circadian clock system may underlie the positive effect of interval fasting on body weight regulation and subjective well-being. Ongoing studies aim at determining other metabolic and non-metabolic targets of timed meal patterning and to what extent the composition of different meals may further affect these functions. While few conclusions can be drawn at this point, it has already been shown that increased cereal/dairy intake during breakfast is associated with better cardiometabolic health. Likewise, early lunch times seem to be a positive predictive factor for weight loss therapy outcomes.

Conclusion

Accumulating evidence suggests an extensive crosstalk between circadian clocks and rhythms and the regulation of energy metabolism. On one hand, synchrony amongst the different components of the circadian network promotes metabolic homeostasis and health. On the other hand, meal timing and nutrient composition affect circadian regulation, thus impacting not only on metabolic functions, but also on further target systems of the circadian clock. The dissection of the molecular underpinnings of this crosstalk will provide interesting therapeutic targets for the prevention and treatment of metabolic disorders in a globalised 24-hour society.

Acknowledgements

HO is a Lichtenberg fellow of the Volkswagen Foundation.

References

Bass J (2012). Circadian topology of metabolism. *Nature* **491**(7424), 348-356.

Blancas-Velazquez A, Mendoza J, Garcia AN *et al.* (2017). Diet-induced obesity and circadian disruption of feeding behavior. *Frontiers in Neuroscience* **11**, 23.

Ecclesiastes **3**:1

Gill S, Panda S (2015). A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metabolism* **22**(5), 789-798.

Landgraf D, Neumann AM, Oster H (2017). Circadian clock-gastrointestinal peptide interaction in peripheral tissues and the brain. *Best Practice & Research: Clinical Endocrinology & Metabolism* **31**(6), 561-571.

Lemmer B, Oster H (2018). The role of circadian rhythms in the hypertension of diabetes mellitus and the metabolic syndrome. *Current Hypertension Reports* **20**(5), 43.

Longo VD, Panda S (2016). Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. *Cell Metabolism* **23**(6), 1048-1059.

Takahashi JS (2017). Transcriptional architecture of the mammalian circadian clock. *Nature Reviews Genetics* **18**(3), 164-179.

The altruism of melatonin

A molecule that protects, heals, and even takes care of the night-shift duties

Russel J Reiter

Department of Cell Systems and Anatomy, UT Health San Antonio, Texas, USA

Sergio Rosales-Corral

Centro de Investigacion Biomedica de Occidente, Instituto Mexicano del Seguro Social, Guadalajara, Mexico

In 1958, when Aaron Lerner isolated and characterised melatonin from bovine pineal tissue, he hoped it would be a treatment for vitiligo – a disease which causes loss of skin colour. When this was proven not to be the case, Lerner almost abandoned research on the molecule. Since then, however, due to the efforts of a troop of inquisitive scientists, a bewildering array of functions have been ascribed to this bewitching molecule. Melatonin predictably evolved several billion years ago in the earliest life forms, bacteria, for protection against toxic chemically reduced oxygen species. Since its creation, melatonin seems to have been preserved in every living organism, both animal and plant.

During its long evolutionary history, melatonin has insinuated itself into many aspects of organ and organismal physiology to the extent that its "fingerprints" are all over subcellular infrastructure. Indeed, it seems possible that cells cannot maintain a healthy lifestyle if melatonin is not present. As melatonin has been loitering in cells for a very long evolutionary period, it also has taken advantage of the opportunities to "learn" to functionally cooperate with other beneficial molecules. Subsequently, one feature that characterises melatonin's actions is diversification.

Melatonin: it's not all in your head

Since melatonin was discovered in the pineal gland, for years it was assumed that this organ was the exclusive source of this serotonin derivative. In the pineal gland of mammals, melatonin is produced in a cyclic manner such that only at night does the gland manufacture significant amounts of this indoleamine. The nocturnal synthesis and release of melatonin is controlled by the master circadian oscillator, the suprachiasmatic nucleus (SCN), whose output is dictated by information it receives about the light-dark environment as detected by highly specialised melanopsin-expressing, intrinsically photoreceptive retinal ganglion cells (ipRGCs) in the eyes.

Unlike many endocrine organs, the pineal gland does not selfishly store any of the product it generates; rather it quickly liberates it into the circulatory and ventricular systems. At night, blood concentrations and especially concentrations in the third ventricular cerebrospinal fluid (CSF) are much higher than daytime values. As a consequence, every cell in an organism that is contacted by blood or CSF is apprised of the light:dark status and can adjust its physiology accordingly, which many do. Within 15 years of Lerner and colleagues (1958) identifying melatonin in the pineal gland, its synthesis was also uncovered in the retina, a neurally-derived tissue. The production of melatonin at this site may not be so extraordinary since the vertebrate eyes and pineal gland have a number of common features. Even in present day vertebrates, remnants of retinal rods and

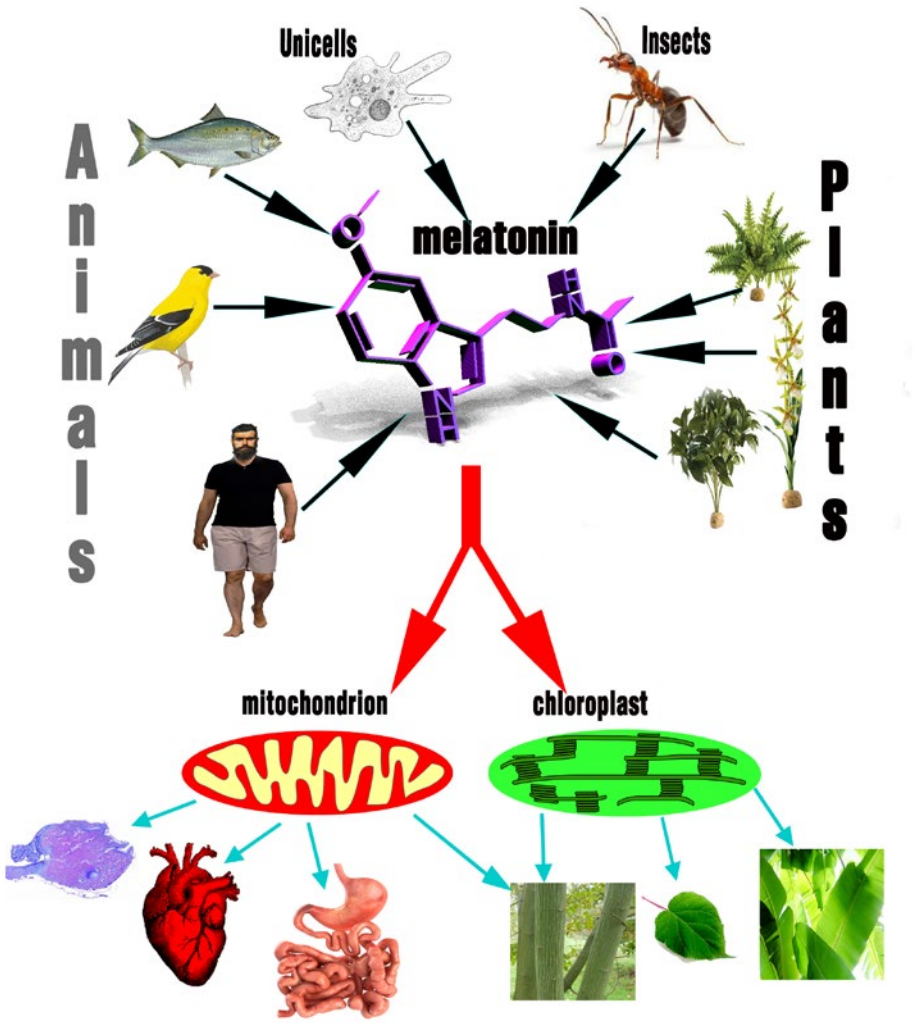


Figure 1. Melatonin is an extremely old molecule having evolved an estimated three billion years ago. It is present in bacteria, unicells, insects, and all vertebrates and plants. Current evidence indicates that primary sites of melatonin synthesis are mitochondria and chloroplasts. Thus, every cell that possesses these organelles may be capable of melatonin production. Equal to its divergent distribution, melatonin is similarly diverse in its functions.

cones are ultrastructurally present in the pineal gland.

Beginning in the 1980s and continuing to the present, high melatonin levels, likely due to its local production, have been identified in a plethora of tissues/cells. Based on these data and immunocytochemical findings related to the intracellular location of a melatonin-forming enzyme, we proposed that melatonin is synthesised in the mitochondria of all cells (Tan *et al.*, 2013). We argued that this is consistent with the Endosymbiotic Theory for the origin of mitochondria. Thus, mitochondria evolved from proteobacteria that were engulfed by early prokaryotic cells for their nutritional value. Eventually, the phagocytosed bacteria, which produce melatonin, established a symbiotic association with the cells that ingested them and they became mitochondria. During this evolutionary process, the evolved organelle retained its melatonin synthesising capability.

If valid, every cell in multicellular organisms may produce melatonin. Recent findings which identified melatonin-forming enzymes in extrapineal cells is compatible with this theory (Suofa *et al.*, 2017). Also, melatonin production occurs in the mammalian oocyte mitochondria (He *et al.*, 2016). Considering that mitochondria of all cells are derived from the oocyte, it is likely that the melatonin-forming potential has been retained in all cells [Fig. 1]. Non-pineal cells use the indoleamine as a defence against oxidative stress in the mitochondria where it is generated. If they release it into interstitial fluid, it acts locally in an autocrine or paracrine manner. While melatonin that escapes cyclically from the pineal gland serves as an essential time giver to many tissues, peripherally generated melatonin is unconcerned with providing timing information but rather has many other critical functions, consistent with its multitasking image.

Melatonin: It is not just for vertebrates

As noted above, the ability of present day animals to produce melatonin is a process inherited from their evolutionary ancestors i.e. bacteria; as a result, all species between bacteria and humans probably likewise engage in the production of this beneficial multifunctional molecule. All organisms that have been tested including unicells, insects, arachnids, non-mammalian vertebrates, mammals, etc., have capitalised on melatonin's favourable actions by synthesising it. The synthetic pathway for melatonin likely did not evolve independently in all these species but rather they acquired this capability during their evolution from more primitive organisms. There are, however, slight variations in the synthetic pathway that the transitional organisms developed possibly because it was more efficient to do so or it afforded them a metabolic advantage. In all vertebrates, tryptophan is a precursor and serotonin is an intermediate metabolite in the trail of melatonin production.

As with mitochondria, the photosynthetic capability of plant cells developed after early eukaryotes engulfed melatonin-synthesising, photosynthetic cyanobacteria for their nutrient value. Over time, the phagocytosed bacteria matured into chloroplasts where they retained their photosynthetic and melatonin-synthesising capabilities. As a consequence, the photosynthetic portions of all green plants produce melatonin at the cellular level in two sites, in their chloroplasts and in mitochondria (Zheng *et al.*, 2017) (Fig. 1). Because they have two organelles to produce melatonin, plant cells generally have higher melatonin concentrations than animal cells.

Melatonin: Physiological diversification

Many scientists and members of the lay public realise that melatonin has sleep-promoting properties, possibly not because of any direct soporific actions but because appropriately timed melatonin administration, via circadian means, "opens the normal sleep gate." This and other observations document the function of melatonin as a circadian and circannual rhythm modulator. This circadian action becomes readily apparent when the pineal-derived day:night fluctuation in blood melatonin levels is interrupted e.g., in shiftworkers, blind individuals, inhabitants of the International Space Station, or individuals suffering from jet lag or social jet lag. In other words, these individuals have trouble sleeping. This action is exclusively a result of a disturbance in the differential release of melatonin over a 24-hour period.

Prior to the discovery of melatonin, some unidentified product of the pineal gland was often linked to reproductive physiology. After Lerner and coworkers (1958) identified the pineal gland as an origin of melatonin, it was soon found that surgical removal of the gland prevented seasonally related reproductive changes in photoperiod-dependent mammals (Hoffman & Reiter, 1965). This melatonin receptor-mediated action is now known to be achieved at the level of the pars tuberalis and the medial basal hypothalamus and is widely accepted to relate to the circadian actions of melatonin. Other functions of melatonin that depend on receptor-mediated processes include its ability to inhibit some aspects of tumour cell proliferation and metastasis, alterations in serotonin release in the retina and activation of antioxidative enzymes, etc. (Hill *et al.*, 2015; Reiter *et al.*, 2017)

Beyond melatonin's functions that involve widely distributed membrane melatonin receptors, the indoleamine does not always rely on an interaction with a receptor/binding site. Melatonin is also a direct reactive oxygen species (ROS) scavenger (Reiter *et al.*, 2017). In this receptor-independent process, ROS, which are often free radicals, are ensnared and neutralised by melatonin. ROS are especially abundantly generated during oxidative phosphorylation (OXPHOS) in mitochondria and during photosynthesis in chloroplasts. Hence, it is highly fortuitous that mitochondria and chloroplasts, which are so involved in the production of partially reduced toxic oxygen species, also produce a highly efficient radical scavenger to detoxify them before they mutilate neighbouring critical macromolecules in the mitochondrial respiratory chain complexes or in the chloroplastic photosynthetic machinery. Oxidative damage to these organelles compromises efficient OXPHOS and photosynthesis, respectively. The functional deterioration to these processes then becomes a violent cycle of more oxidative destruction accompanied by greater ROS production. Other high free radical-generating situations where the direct scavenging actions and the indirect antioxidant functions of melatonin come into play include the following: ionising radiation exposure, obesity, ischaemia/reperfusion injury, cytokine production, toxin and toxic drug exposure, severe inflammation, etc. (Anderson & Maes, 2014; Cipolla-Neto *et al.*, 2014).

In addition to the manufacture of melatonin by mitochondria, these organelles avidly take up endogenously produced or exogenously administered melatonin from blood or other bodily fluids. This process may involve specific active transporters in the cell and mitochondrial membranes allowing the latter to retain much higher concentrations than exist in other subcellular structures (Reiter *et al.*, 2017). This mitochondrial targeting by melatonin helps to explain its high efficiency as an antioxidant. Related to this, the pharmaceutical industry has been designing mitochondria-targeted antioxidants for years realising they could be useful in modifying the cause of many diseases that have a free radical component. When these synthetic antioxidants were compared with melatonin in reference to their oxidative stress-quenching potential, they were no better, and for some responses less effective, than naturally occurring and non-toxic melatonin.

In plants, several functions have been described for melatonin. Any process that stresses a plant, e.g., excessive heat or cold, drought, increased salinity, etc., induces a rapid rise in the levels of melatonin, which are used to quell the greatly augmented numbers of ROS produced in response to the stress (Reiter *et al.*, 2015). The induction of melatonin synthesis under stressful circumstances may be a feature of animals as well. Besides its synthesis, plants also take up melatonin through their root system. The higher melatonin concentrations in plants compared to those in animals may be especially beneficial as a protection against ROS since plants are sessile and cannot avoid stressful stimuli when they occur. A second identified action of melatonin in plants is as a growth promoter. Incubating seeds in a melatonin-containing solution before germination or spraying it on plants during their early development results in larger and more productive plants. Since melatonin receptors have yet to be identified in plants, these observed actions are presumed to be receptor-independent.

Finally, melatonin aids plants in resisting diseases. The actions described, especially the inducibility of melatonin in stressed plants, could be highly significant during global climate change if plants are genetically engineered to produce elevated levels of this protective indoleamine.

Epilogue

Melatonin is uncommonly effective in quenching renegade radicals. These brigands typically molecularly devastate cells and weaken their defences against the development of pathologies and death. By shielding mitochondria/chloroplasts from the large-scale damage inflicted by ROS, melatonin improves the viability and/or productivity of organisms. Thus, the significance of the pronounced antioxidant potential of melatonin cannot be overstated. There are many other noteworthy actions of melatonin that have justifiably attracted attention. Its ability to adjust the circadian clock, regulate seasonal reproduction, its oncostatic actions and anti-inflammatory effects, and its protection against toxins, all assist melatonin in resisting functional deterioration and diseases of cells. In view of the diversity of these observed functions, it seems likely that they may be merely epiphenomena of more basic actions of this indoleamine, which are yet to be uncovered.

Melatonin's functional "toolkit" is extraordinarily large. This may relate to its three billion year longevity, an interval during which it developed a working relationship with many other essential molecules all of which provide an advantage to organisms. Viewed in this context, the altruism of melatonin should not be underestimated.

References

Anderson G, Maes M (2014). Local melatonin regulates inflammation resolution: a common factor in neurodegenerative, psychiatric and systemic inflammatory disorders. *CNS & Neurological Disorders - Drug Targets* **13**, 817-827.

Cipolla-Neto J, Amaral FG, Afeche SC *et al.* (2014). Melatonin, energy metabolism, and obesity: a review. *Journal of Pineal Research* **56**, 371-381.

He C, Wang J, Zhang Z *et al.* (2016). Mitochondria synthesize melatonin to ameliorate its function and improve mice oocyte's quality under in vitro conditions. *International Journal of Molecular Sciences* **17**, E939.

Hill SM, Belancio VP, Dauchy RT *et al.* (2015). Melatonin: an inhibitor of breast cancer. *Endocrine Related Cancer* **22**, R183-R204.

Hoffman RA, Reiter RJ (1965). Pineal gland: influence on gonads of male hamsters. *Science* **148**, 1609-1611.

Lerner AB, Case JD, Takahashi Y *et al.* (1958). Isolation of melatonin: the pineal gland factor that lightens melanocytes. *Journal of the American Chemical Society* **80**, 2587.

Reiter RJ, Rosales-Corral SA, Tan DX *et al.* (2017). Melatonin as a mitochondria-targeted antioxidant: one of evolution's best ideas. *Cellular and Molecular Life Sciences* **74**, 3863-3882.

Reiter RJ, Tan DX, Zhou Z *et al.* (2015). Phytomelatonin: assisting plants to survive and thrive. *Molecules* **20**, 7396-7437.

Tan DX, Manchester LC, Rosales-Corral SA *et al.* (2013). Mitochondria and chloroplasts as the original sites of melatonin synthesis: a hypothesis related to melatonin's primary function and evaluation of eukaryotes. *Journal of Pineal Research* **54**, 127-138.

Suofu Y, Li W, Jean-Alphonse FG *et al.* (2017). Dual role of mitochondria in producing melatonin and driving GPCR signaling to block cytochrome c release. *Proceedings of the National Academy of Sciences of the United States of America USA* **114**, E7997-E8006.

Zheng X, Tan DX, Allan AC *et al.* (2017). Chloroplastic biosynthesis of melatonin and its involvement in protection of plants from salt stress. *Sci Rep* **7**, 41236.

Honing into a PhD starting with the Undergraduate Prize

Paulina Lukow

University of Surrey, UK
& King's College London, UK

I was recently honoured with the Undergraduate Prize from The Physiological Society for my results in physiology modules and my final year dissertation project.

I have always been fascinated with processes too complex to understand by looking at a single mechanism. The first time I learned about such phenomena was during my physiology courses in the first two years of my degree. Understanding these required zooming into the cell to explore its genetics and biochemistry, and then zooming out on the intercellular interactions making up a tissue's local microenvironment, which would then influence the functioning of a whole system. It wasn't long before I became amazed by neuroscience, where several nearly simultaneous molecular events, often distant spatially, underlie complex higher functions such as behaviour or emotion.

To become involved in neuroscientific research, I pursued a placement at Karolinska Institutet between the second and final years of my degree. I worked on the generation of *in vitro* neural models from human pluripotent stem cells. These cells can be derived from the inner cell mass of a structure which emerges within the first week after ovum fertilisation. Alternatively, they can be created from adult somatic cells. They can develop into any cell within a human body. Such cells can be used for preclinical disease investigation and therapy development.

Paulina Lukow with her Undergraduate Prize (Photo by The University of Surrey).

My colleagues were using these models to study psychiatric disorders such as schizophrenia or bipolar disorder. I have always wanted my research to be meaningful, and I soon felt very passionate about psychiatry. Thus, towards the end of my placement, I keenly took the opportunity to get involved in a project studying the influence of adolescent stress on psychiatric outcome.

Having identified statistical data analysis as a key skill in research, I was hoping my final year dissertation topic would allow me to learn it. Fortunately, the project I got allocated was the "Analysis of sleep spindle oscillations in the cortex of rats." The task was to characterise a specific rhythmic activity of the non-rapid eye movement stage of sleep, called the sleep spindle. The aim was to describe its parameters in the rat model, commonly used in sleep research, and compare it to the literature on human sleep. I was very lucky to work under Julie Seibt's supervision, as she helped me throughout my project.

These various experiences allowed me to identify the aspects of scientific work I enjoyed most, and I integrated them in my search for a PhD. I was extremely happy to be admitted for a PhD at King's College London to investigate the development of psychosis, combining data analysis, complex neuroscience and a sense of meaning in a single project. As I am facing my doctoral programme, I feel grateful for the recognition of the Undergraduate Prize and encouraged to continue setting myself more and more ambitious goals.

I would like to thank Rita Jabr, The Physiological Society Representative at the University of Surrey once again for putting me forward, and my physiology lecturers without whom I couldn't have achieved such results. I would also like to acknowledge Julie Seibt for her invaluable help throughout my dissertation project.

Practical tips for public engagement: Lessons from The Phyiological Society's training day

Miriam Hurley

University of Leeds, UK

Why does a researcher devote endless time and energy to answering a scientific question? One reason is to conquer the challenge of scientific research in order to uncover the mysteries of our own physiology. Equally important is the great benefit that our discoveries can bring to society. To enable this, it is imperative to communicate the outcomes of the research that we undertake to the general public. In June, The Physiological Society's Public Engagement Training Day gave attendees practical tips for starting public engagement.

Over the course of the day, we were challenged to consciously consider the words and phrases that we use when communicating our research. For example, what is the most accessible definition of heart failure? We were asked to explain our research in one sentence, either to our peers, a member of the public, or a family member. It surprised me how difficult this was. We had to be aware of who we were talking to and the environment that we were talking within, whilst simultaneously being engaging and succinct.

Across the course of the day we heard from many working within the field of science communication as to how they undertake public engagement. For example, we heard about science communicated in the form of informative videos, interactive activities such as "The Race to Sleep" board game and the presentation of science through history. We learnt that the aim of such an event is to create a dialogue about physiology in a way that is fun, interactive and educational. Specifically, when establishing a public engagement event we were advised to practice our event beforehand and use evaluation tools afterwards to obtain invaluable feedback. This would enable the continual development of the event to achieve the aim of communicating science in the most accessible way.

The day ended with an opportunity to consider our own scientific outreach as we asked ourselves "what's next?" I pledged to "establish a public engagement event relating to my research". I organised an event on 12 October 2018 to promote Physiology Friday. With the use of smartphone microscopes and visual impairment glasses, we discussed with students at The University of Leeds, how the technological advancement in microscopy has enabled a greater understanding of our own physiology. This event was in partnership with The Physiological Society, who generously provided funding, resources, and support to enable my pledge to be fulfilled.

I challenge you to make a pledge, inspired by the values of The Physiological Society, so that we can give our scientific research the voice it deserves and promote the value of STEM subjects to the next generation. Email **outreach@physoc.org** with any questions or ideas.

> "We learnt that the aim of such an event is to create a dialogue about physiology in a way that is fun, interactive and educational"

Lab Research 101: Top tips for undergraduates starting lab research

Juliette Westbrook

University of Oxford, UK

Attendees of the Summer Studentship Training Day.

As undergraduates, we learn the nuts and bolts of physiology, but not all the skills required for lab research. We carry out group research revolving around well-tested scientific principles. However, we rarely have the opportunity to work independently on research. To remedy this knowledge gap, The Physiological Society organised a training day focused on reading scientific papers, analysing data, good lab practice and data presentation. We also had the opportunity to meet like-minded individuals passionate about physiology and research.

One session focused on the importance of having a well-organised lab book. My experiment tested 22 participants, and I usually would not get a chance to analyse data until a few days after they had participated in the experiment. Recording data and problems that occurred on the spot made data analysis and lab report writing smoother and more accurate.

At the training day, we also had the opportunity to learn about data analysis and presentation, in relation to research carried out. Often in undergraduate labs, students are given a set of analyses to run. We use common tests on statistical software that we are familiar with. In the training day, we explored the best type of statistical analysis to use when analysing our data sets, and how to best represent and present data findings either graphically or pictorially. This was useful, as we learnt how to identify the optimal analysis to carry out on our data sets, depending on the nature of our research.

Training day attendees also learnt the importance of scientific communication with people who are not necessarily from scientific backgrounds. Lay abstracts, alongside scientific abstracts are used to explain research to people outside of the field. The training day taught us how to communicate effectively, without using key words or abbreviations, but still explaining key principles in a clear and efficient way. My advice to people writing a lay abstract is to write it from scratch, as opposed to trying to "translate" an already completed scientific abstract. Furthermore, when it's finished, ask someone who does not work in the lab, or is not familiar with science, to read your abstract. If they understand your research from what you have written, then your lay abstract is probably sufficient!

At the end of the training day, we were all asked to make pledges about our projects. My pledge was "to be inspired and inspire others." I have always been interested in medical psychology and neurophysiology, working in a preclinical lab in King's College Hospital on projects about sickle cell disease, asthma, and others. However, before undertaking the Summer Studentship, I was not sure whether I wanted a career in research. My placement inspired me to continue my career in academia. I am grateful to have worked at the King's College London Muscle and Respiratory Lab, under the supervision of Victoria MacBean.

The second aspect of my pledge was to inspire others. In 2015, I was part of a panel of schoolchildren in years 11-13 that discusses physiology and physiological techniques. I am passionate about outreach as it gives younger generations an early insight into scientific careers, opportunities that they did not consider undertaking or did not think that they were capable of doing. To give current panel members the chance to experience research, a lot of the participants in my experiment were the panel members. When panel members came in, I was able to explain everything about the research to them, as well as speak to them about university and careers. I hope that I was able to inspire the next generation of young researchers to take up a science degree and career in the future.

Overall, the training day allowed attendees to leave with the confidence that they would be able to undertake their research projects independently. It gave us confidence in our ability to carry out the research, and take our newly learned skills and put them into practice, whilst simultaneously being well organised, efficient, and able to independently overcome any problems encountered during our research. Given that most research conducted in labs during undergraduate degrees is completed with other people, having confidence in the decisions you make about how research is conducted, is of the utmost importance. Both learning from mistakes and achieving through successes make you a better researcher, and by having the confidence to make independent decisions, this gives us the opportunity to develop as researchers.

Becoming a clinical academic physiologist: Reflections 20 years on, from an Undergraduate Prize winner

Robert W Hunter

Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, UK

In physiology – as in life – words matter. One of the things that attracted me to physiology was that it is a discipline that is very careful with its words. In our first undergraduate physiology lecture as medical students, we learned from Roger Carpenter that physiology was the study of *"whys"* and *"wherefores"*. *Why* does the kidney reabsorb more salt after we vomit? Because aldosterone activates sodium channels in the collecting ducts. *Wherefore*? Because this will restore circulating volume. I found the *wherefores* more engaging: understanding how systems operate to defend homeostasis at the level of the whole organism is a fascinating pursuit, and one to be highly valued in the era of molecular biology (Lemoine & Pradeu, 2018).

Fast-forward 20 years and I'm now an academic nephrologist studying the molecular determinants of renal tubular function. Recently, I have been wrestling with a subtle semantic distinction. Am I an *academic clinician* or a *clinical academic*? Do I see myself as a doctor who sometimes does science or a scientist who sometimes treats patients? As a medic, am I even allowed to call myself a scientist? Why on earth should a medic do experiments in a wet-lab when a "proper scientist" could do the same work more rigorously? I love academic medicine but I – and many others – find it a hard career to pursue because it is so easy to succumb to the imposter syndrome.

I was awarded an Undergraduate Prize for my degree project ("Depolarisation-induced pH gradients in patch-clamped snail neurones" with Christof Schwiening in Cambridge). I had really enjoyed my time in the department and had definitely caught the physiology bug. I loved that reproducible data could emerge from a combination of the sophisticated (the hideously complicated patch-clamping apparatus) and the unsophisticated (the snails were foraged from the wild and we dissociated the ganglia at ~37 °C by shoving Eppendorfs down our socks). I loved that simple models could explain current traces in terms of pump and channel activity. I loved that these models could be refined by iteratively testing predictions in the lab. However, I don't think I believed that I could make a career from studying physiology. Wouldn't it be better to leave all that to the proper scientists?

The Undergraduate Prize validated what we had been doing; it allowed me to think that perhaps I *could* become a physiologist. And of course when, some years later having completed my medical degree, I decided that I would like a career in physiology it was a very useful thing to have on my CV as I applied for PhD funding.

> "It is difficult to think of any other medical specialty in which the interplay between basic physiology and clinical medicine is so immediate"

I have since completed a PhD as part of the Edinburgh Clinical Academic Track (ECAT) scheme for trainee clinical academics. I studied renal tubular physiology in a model of apparent mineralocorticoid excess with John Mullins, Linda Mullins and Matt Bailey. I spent three happy years studying ion fluxes again – not in the snail neurone this time but in the mammalian nephron (Hunter *et al.*, 2018). I recently started as a Wellcome-funded Career Development Fellow and now spend most of my time studying communication between renal glomerular and tubular cells *via* extracellular RNA. (We are trying to define *why* and *wherefore* the renal tubules respond to RNA signals from the glomerulus.)

When I'm not in the lab I work as a nephrologist. It is difficult to think of any other medical specialty in which the interplay between basic physiology and clinical medicine is so immediate. Many of the problems faced by patients with kidney disease are a direct consequence of deranged fluid-electrolyte physiology: oedema, hyperkalaemia, hypertension, acidosis. Not only can we understand exactly why our patients are unwell, but we can also make them better using therapies that specifically subvert basic renal physiological processes. Clinical practice evolves, driven by basic physiological research. For example, over the past decade we have learnt how oedema in nephrotic syndrome is caused by the activation of sodium channels in the collecting ducts (Svenningsen, 2009). We can treat this using sodium channel blockers, such as amiloride. Or to take another example: decades of research into the molecular mechanisms of renal tubular glucose transport are now culminating in the introduction of sodium-glucose co-transporter inhibitors into widespread clinical practice, with the potential to prevent death and disability in millions of patients with diabetes and kidney disease.

It is this potential to be truly transformative that attracts me to basic physiology research. Despite the huge advances that we have made, there are still clinical problems that we cannot solve. Many patients with glomerular disease will progress inexorably towards kidney failure and a life of dialysis treatment or kidney transplants. We don't understand why this should be. That is the problem that our lab is trying to address, by first understanding how glomerular disease spreads to involve other kidney compartments.

I am extremely grateful to The Physiological Society for encouraging me at an early stage to pursue a career in basic physiology research. They helped me to consider myself as much a physiologist as a clinician: a *clinical academic*. Medical students often say that they chose medicine in order to "make a difference" or "help others". I would encourage any student - so motivated - to consider a career in fundamental physiology research. Basic scientists have had a pervasive influence on modern medicine (think Banting & Best, Cesar Milstein, Bob Edwards, Dorothy Hodgkin, Peter Medawar, Marie Curie). *Why* should a medical student today wish to become a clinical academic physiologist? Because is it a fun, rewarding and stimulating career. *Wherefore*? Because he or she could advance our understanding of physiology in a way that opens up new ways to treat disease, and so help people around the globe.

References

Lemoine M & Pradeu T (2018). Dissecting the meanings of "physiology" to assess the vitality of the discipline. *Physiology* **33**, 236–245.

Hunter RW, Craigie E *et al.* (2014). Acute inhibition of NCC does not activate distal electrogenic Na^+ reabsorption or kaliuresis. *American Journal of Physiology - Renal Physiology* **306**, F457-467

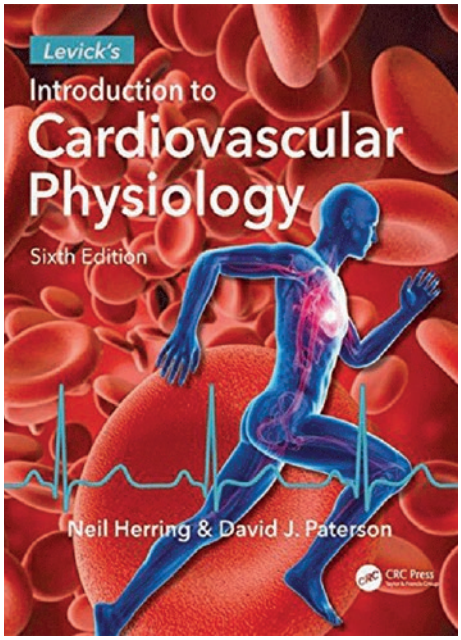
Svenningsen P, Bistrup C *et al.* (2009). Plasmin in nephrotic urine activates the epithelial sodium channel. *Journal of the American Society of Nephrology* **20**, 299-310.

Levick's Introduction to Cardiovascular Physiology

A favourite cardiovascular textbook gets better

David Eisner

The University of Manchester, UK



Neil Herring & David J. Paterson
CRC Press; 6th edition, 2018
ISBN: 9781498739849

A commonly accepted index of ageing is that police officers seem young. For me, a more relevant one might be that I can remember the original publication of this book, now in its sixth edition, in 1991. The current edition, authored by Neil Herring and David Paterson, includes a tribute to the author of the first five editions, Rod Levick.

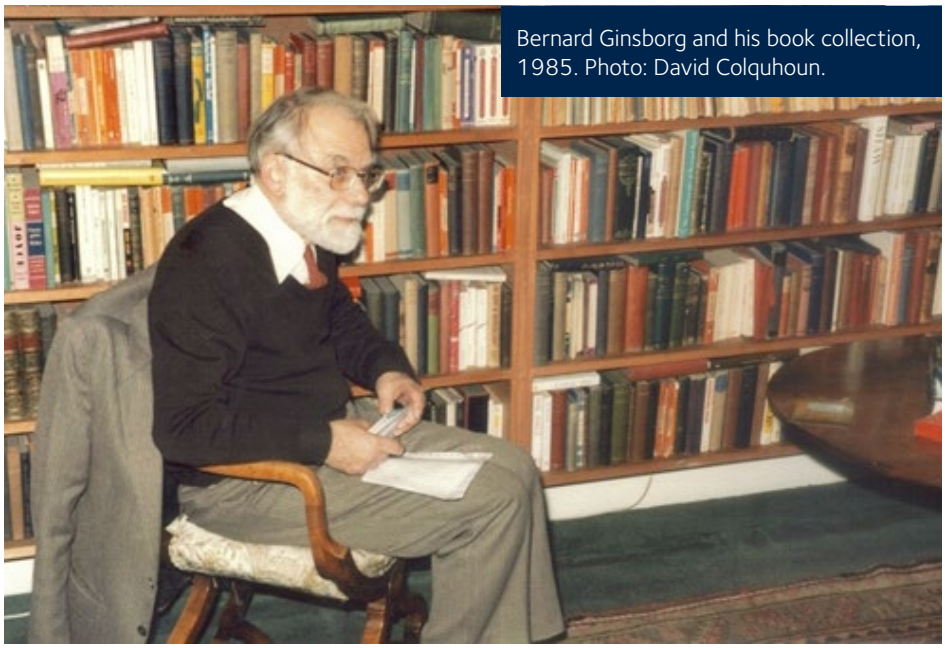
Writing a book on cardiovascular physiology must be no easy task. A generation ago, it might have been possible for a physiologist to be conversant with much of cardiovascular physiology. Today, the subject has split into enormous and diverse subfields. How much does a jobbing cardiac cellular electrophysiologist know about areas such as capillary function, central control, endothelial biology and so forth? Indeed, keeping up with calcium cycling alone is a full-time business for me. It is very much to the credit of Levick (originally), and now Herring and Paterson, that they have the level of scholarship required.

One of the strengths of the original book was that it managed to serve many "markets." This has been retained in the current version. It covers the cardiovascular system from the cellular properties of cardiac and vascular smooth muscle myocytes through organ level physiology and central regulation. While it provides a good introduction to the subject for undergraduates, it is equally useful for those starting a PhD. Indeed, in today's multidisciplinary world, it makes a great introduction to cardiovascular physiology for the non-physiologist entering the cardiovascular field who wishes to understand the relevant physiology. It also does an excellent job of integrating the various systems. As someone who works at the cellular end of cardiac muscle, I benefit from regular reminders of the importance of interactions with blood vessels, the brain, and other systems. In particular, the chapter on coordinated cardiovascular responses helps knit things together very well.

The authors have very sensibly kept most of the text and diagrams from the previous edition. Many of the diagrams have been freshened with the use of full colour. Importantly, two new chapters have been added which introduce the experimental methods used in modern cardiovascular research. These will be of tremendous help in giving students an idea of how the results described in the book were obtained.

"Indeed, in today's multidisciplinary world, it makes a great introduction to cardiovascular physiology for the non-physiologist entering the cardiovascular field who wishes to understand the relevant physiology"

The Kindle version of the book is beautifully formatted. Not only is it very convenient to search for information, but it is weightless! Alternatively, purchase of the paper version provides a code for an e-book as well. Inevitably, it is difficult for a book covering the whole cardiovascular system to keep up with the pace of research. Having heard Maiken Nedergaard's lecture at the conference Europhysiology 2018, the subject of the lymphatic drainage of the brain would benefit from more attention in the seventh edition. This, however, is very much a minor complaint. All in all, the authors deserve the gratitude of all their colleagues and students for updating an old favourite.



Bernard Ginsborg and his book collection, 1985. Photo: David Colquhoun.

Obituary:
Bernard Ginsborg 1925–2018

Born in London, Bernard Ginsborg graduated in physics from the University of Reading in 1948, followed by a PhD on eye movements in 1953. His life's work on membrane biophysics began when he joined the Biophysics Department at University College London. In 1957 Bernard moved to the MRC National Institute in Mill Hill when Walter Perry recruited him to join the scientific staff. In 1958 he moved again, this time to the University of Edinburgh when Perry became the Professor of Pharmacology there. Bernard ascended the academic ladder quickly from a Lectureship in 1962, to a Readership in 1964 and finally to a Personal Chair in 1976. He served as the Head of the Pharmacology Department from 1980 to 1984.

Over four decades he published research papers on numerous biophysical themes with several collaborators. His papers stand as models of scientific writing. The range of topics was wide and included human eye movements, the biophysics of invertebrate muscle membranes, synaptic transmission in amphibian sympathetic ganglia, presynaptic inhibition at the mammalian neuromuscular junction, dopamine receptors on insect salivary gland cells and ion channel behaviour in human neuroblastoma cells.

Most of Bernard's papers were published in *The Journal of Physiology*. His first paper in *The Journal* described the results of his PhD project with RW Ditchburn, and was remarkable in several ways. First, it reported the measurement of tiny involuntary movements of the eyes during a subject's fixed gaze on a stationary point. To measure such minute eye movements in a human subject is a measure of Bernard's skill as an experimentalist. The second remarkable feature of this paper is that nearly all of the measurements were made on a single subject – Bernard himself. He called these tiny eye movements "flicks" but they are now called microsaccades and are still being studied in the field of visual perception.

After Bernard joined the Biophysics Department at University College London he collaborated with Paul Fatt in a study of the excitability of crustacean muscle fibres. The impetus for this project was a paper in 1953 by Paul Fatt and Bernard Katz showing that the sodium hypothesis of Hodgkin and Huxley to explain excitability of nerve axons did not apply to crustacean muscle fibres. They concluded that "the mechanism of the action potential, and the species of ions involved in the movement of charge across the membrane remain a puzzling problem." In 1958 Paul Fatt and Bernard solved the puzzle when they discovered that electrical stimulation of the crustacean muscle membrane elicited a calcium action potential. Their paper was a turning point in the history of neuroscience. Before 1958 the existence of voltage-gated sodium channels dominated the understanding of cell excitability. The existence of voltage-gated calcium channels transformed our understanding of cellular signalling.

When Bernard left the Biophysics Department he carried its powerful imprint of high standards and in all of his later work he maintained a strong analytical approach. He also obeyed the golden rule that his name would never appear as a listed author on a paper unless he had played a significant part in the work reported.

Working with Bernard was challenging, enlightening, productive and great fun. He had a marvellous sense of humour, often aimed at his own foibles. In the lab Bernard was committed to all of the demands of the experiments and writing papers was his speciality. He had a superb understanding of electrophysiology and its literature, and was an outstanding editor of *The Journal of Physiology*.

"When Bernard left the Biophysics Department he carried its powerful imprint of high standards and in all of his later work he maintained a strong analytical approach"

Bernard was wary of authority especially in the offices of bankers, lawyers and doctors. On one occasion he ended a meeting with a consultant who was giving him advice about healthy living by telling him, "You just want to control the way I die." Bernard, however, was the soul of old-fashioned courtesy and generous with his time and help. His modesty notably outshone his intellectual brilliance.

It was a huge privilege and honour to work with him and, even more so, to become his friend. It was wonderful to listen to stories about his experiments in the Biophysics Department in London. He had a fund of tales about scientists who worked there, especially Liam Burke, Paul Fatt, Bob Martin, Ricardo Miledi, John Nicholls, Rolf Niedergerke, Bernard Katz and Sally Page.

In one of his novels PG Wodehouse, referring to a rather dim character, writes: "If men's minds were like dominoes, surely his would be the double blank." In Wodehouse's classification Bernard would be, without doubt, the double six, both as a scientist and a man. Bernard, my highly valued collaborator and very dear friend, enriched my life. I am sure that he enriched the lives of others too.

Written by Randall House
Honorary Member of The Physiological Society

PHYSIOLOGY 2019
Your annual conference

First class science, exciting keynotes, and unmissable networking opportunities.

Enjoy a Scottish welcome with friends old and new in the historic city of Aberdeen.

Registration opens 1 January 2019
www.physoc.org/physiology2019

Physiology 2019
8 - 10 July 2019
Aberdeen Exhibition and Conference Centre, UK

The Physiological Society