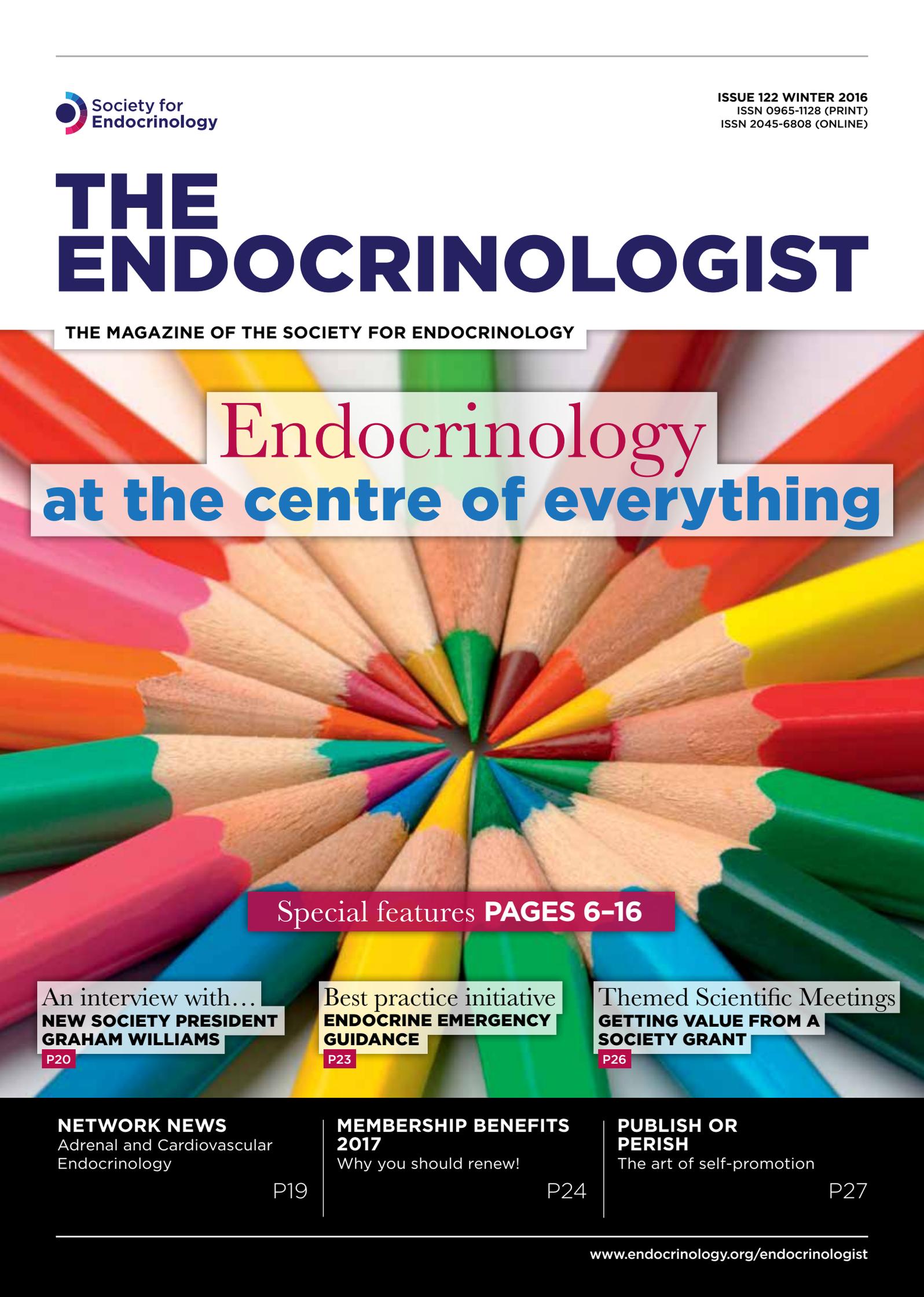


THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY



Endocrinology
at the centre of everything

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A word from THE EDITOR...



Neither this magazine, nor the Society it represents, exists to push any kind of political message. However, as I write this on a rainswept evening a few days after the Society for Endocrinology BES meeting in Brighton, I think it's fair to say we are living in interesting and rather trying times. The era of 'post-truth' politics seems to be upon us and, as the rancorous US election staggered and collapsed into its shocking finale, if the media are to be believed, anger, fear and uncertainty are all we have.

How to respond to this dark wall of negativity? I'm with Michelle on this one: 'When they go low, we go high.' What was on offer at SfE BES 2016 gave me great hope that many of you are of the same mind. It was a delight to see intelligent, rational, questioning science, coupled with a compassion and determination to make things better, and applied to a whole host of problems. Here were endocrinologists, truly at the centre of everything.

This issue continues on the same theme. We have several articles from the world of cancer biology. These remind us that molecular endocrinology is at the heart of so many effective treatments and that clinical endocrinologists are always there to pick up the pieces successfully when unintended organ damage occurs. Look out too for a series of reports on the value of talking to people face to face, be it other scientists in your field, like-minded European clinicians with a passion for training, or patients with acromegaly who need help and support.

Finally, please do read Amir Sam's interview with our new President, Graham Williams. In an era of so much electoral angst, here is one result which we should all actively celebrate. I dare you not to be uplifted and encouraged by what Graham has to say.

So stay positive and 'keep on keeping on'. It's not long until the days start lengthening and the snowdrops are up.

BEST WISHES

TONY COLL

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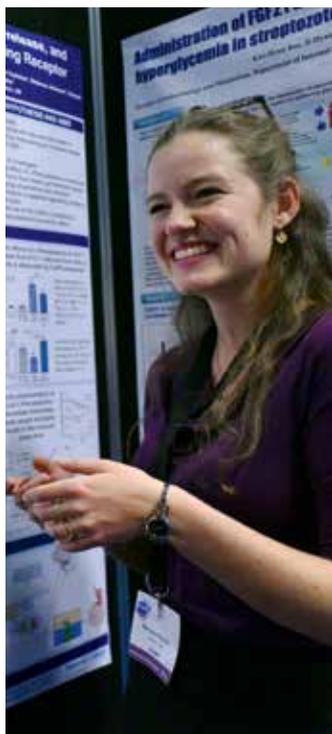
Become a contributor... Contact the Editorial office at endocrinologist@endocrinology.org

The Society welcomes news items, contributions, article suggestions and letters to the Editor. We would also like to hear your feedback on this issue of the magazine.

Deadline for news items for the Spring 2017 issue: **12 December 2017**.

Deadline for news items for the Summer 2017 issue: **20 March 2017**.

Front cover image ©SHUTTERSTOCK



BUZZING IN BRIGHTON: GREAT SUCCESS FOR SfE BES 2016

It was great to welcome so many of you to Brighton for this year's Society for Endocrinology BES conference. The event was a resounding success, with 1,100 delegates, 420 abstracts presented, 10 plenary sessions, 12 symposia, 9 'Meet the Expert' gatherings, plus 3 'Futures' and 'Skills' sessions. It was a fitting tribute to the Society's 70 years of support for endocrinologists! You can enjoy a full round up of the highlights in the next edition of *The Endocrinologist*.



SOCIETY CALENDAR

9 January 2017
OBESITY UPDATE
London

27 January 2017
**NATIONAL CLINICAL
CASES MEETING**
London

20–22 March 2017
CLINICAL UPDATE
Birmingham

20–21 March 2017
**ENDOCRINE NURSE
UPDATE**
Birmingham

[www.endocrinology.org/
events](http://www.endocrinology.org/events) for full details

SOCIETY SUPPORTED EVENTS

2 February 2017
**19TH
CLINICOPATHOLOGICAL
CONFERENCE ON
PITUITARY DISEASE**
London

NEW MEMBER BENEFITS FOR 2017

FREE PUBLISHING IN JOE, JME AND ERC

A new Society initiative makes it easier for members to publish in *Journal of Endocrinology*, *Journal of Molecular Endocrinology* and *Endocrine-Related Cancer*.

If a paper's corresponding author is a Society member, we will waive all charges for publishing supplementary data or printing in colour (so long as colour is essential for your results to be understood). Because these journals don't have any page charges, it means **you can publish in them completely free of charge**, unless you want open access publication or non-essential colour printing.

All you need to do is to provide your Society affiliation when you submit your paper.

Remember, members already benefit from discounted open-access charges when publishing in *Endocrine Connections* and *Endocrinology, Diabetes & Metabolism Case Reports*.



DISCOUNTED ESE MEMBERSHIP

All Society for Endocrinology members now benefit from discounted membership for the European Society of Endocrinology. This is part of ESE's National Affiliated Membership scheme and applies to individuals who are existing ESE members as well as those joining for the first time.

For details, including fees and benefits, see www.es-hormones.org/membership

WITH THANKS



Stephen O'Rahilly finished his term of office as President of the Society in November. Our grateful thanks go to him for all his work and input during his tenure.

You can read an interview with his successor, Graham Williams, on page 20.

CONGRATULATIONS

Andrew Hattersley (Exeter) has been awarded the European Association for the Study of Diabetes (EASD)-Novo Nordisk Foundation Diabetes Prize for Excellence.

WITH REGRET

We are sorry to announce the death of Isabel Forsyth, who was a Senior Member of the Society, and formerly Head of the Department of Endocrinology and Physiology at the National Institute for Research in Dairying, Reading.

GRANT AND PRIZE DEADLINES

15 December 2016
TRAVEL GRANTS

11 March 2017
SUMMER STUDENTSHIPS

31 March 2017
**PUBLIC ENGAGEMENT
GRANTS**

15 April 2017
**REGIONAL CLINICAL
CASES MEETING GRANTS**

17 April 2017
**PRACTICAL SKILLS
GRANTS**

27 May 2017
EARLY CAREER GRANTS

27 May 2017
EQUIPMENT GRANTS

31 May 2017
**THEMED SCIENTIFIC
MEETING GRANT**

[www.endocrinology.org/
grants](http://www.endocrinology.org/grants) for full details of
all Society grants

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via the members' area on the Society home page, www.endocrinology.org. *Endocrine Connections* and *Endocrinology, Diabetes & Metabolism Case Reports*, the Society-endorsed case reports publication, are open access (OA) and free to all.



JOURNAL OF ENDOCRINOLOGY

Metabolic effects of 5 α -reductase 1 disruption

Isoforms of 5 α -reductase regulate the production of steroid hormones and metabolites. In male mice, global deletion of 5 α -reductase type 1 resulted in obesity and insulin resistance, with increased susceptibility to liver steatosis, fibrosis and hepatocellular carcinoma, but questions remained as to the relative contribution of androgens or glucocorticoid signalling in phenotype development.

Livingstone *et al.* therefore examined the role of 5 α -reductase type 1 deficiency in females on metabolic parameters, using a transgenic knockout approach. Altered

stress responses were observed in females with 5 α -reductase type 1 deficiency, with decreased corticosterone production in response to restraint, and decreased corticotrophin-releasing hormone (CRH) and arginine vasopressin transcript expression in hypothalamic nuclei, as well as reduced CRH receptor expression in the pituitary. Metabolic profiling showed increased body weight and adiposity in 5 α -reductase knockout females, with changes in hepatic weight and lipid profile with ageing.

Read the full article in *Journal of Endocrinology* **232** 29–36

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Interleukin-6 in obesity-related bone loss

Higher body weight is beneficial for bone formation. However, excess fat (obesity) predicts reduced bone density and, in mice, a high fat diet (HFD) causes trabecular bone loss. Osteoblasts and adipocytes originate from the same progenitor cells and obesity increases the differentiation of adipocytes and decreases that of osteoblasts. A clue to the mechanism could be that obesity can be considered a chronic inflammatory condition, and that there is an increase in circulating inflammatory cytokines, including interleukin-6 (IL6).

Using *IL6* knockout mice (*IL6*^{-/-}), Wang *et al.* investigated the pathological role of IL6 in HFD-induced bone loss. Although the skeletal phenotype appeared

normal, *IL6*^{-/-} mice had higher trabecular thickness. The knockout mice were protected against the trabecular bone loss seen in response to an HFD. Osteoblastogenesis (assessed by *Runx2* and collagen $\alpha 1$ mRNA expression) was maintained in the HFD *IL6*^{-/-} mice, while adipocytogenesis and fat deposition were lower than those seen in wild type mice.

This study suggests that *IL6* gene deficiency can antagonise HFD-induced bone loss, possibly by increasing osteoblast development while limiting adipocytogenesis, and presents a potential therapeutic target.

Read the full article in *Journal of Molecular Endocrinology* **57** 161–170

ENDOCRINE-RELATED CANCER

Women in cancer

In a departure from recommending a specific article, we draw your attention to November's issue of *Endocrine-Related Cancer*, which includes a special section entitled 'Women in cancer'. This contains personal profiles from senior and prominent female cancer researchers, detailing their career paths and perspectives on their cancer specialities. It also features thematic reviews of the researchers' areas of interest.

The articles are accompanied by an introduction from Guest Editors Deborah Marsh and Charis Eng, who explain how the scientists featured in the section were recruited by a process of collecting nominations for outstanding mid-career women in endocrine cancer research.

The section provides an interesting and inspiring read, giving insights both into the participants' career paths and into the excellence of their science.

Read the full section in *Endocrine-Related Cancer* **23** E5–E7, P5–P35, T85–T178

ENDOCRINE HIGHLIGHTS

A summary of papers from around the endocrine community that have got you talking.

Neural correlates of ticklishness in the rat

How are we ticklish? The answer to this question has long eluded us. Ishiyama & Brecht's intriguing study has further explored the origins of modalities of ticklishness.

Rats emit a 50MHz vocalisation when tickled, which can be taken as a primitive form of joy. This vocalisation was used to map neuronal firing rates in response to different sensory inputs – via touch, play and the effects on this of anxiety. In this way, the researchers correlated the sensory input and tickling response to neuronal centre output. This study mapped the tickling response to the somatosensory cortex, showing similar vocalisations and tickling behavioural patterns can be found in rats and humans.

Read the full article in *Science* **354** 757–760



CLINICAL ENDOCRINOLOGY

Adrenal insufficiency with opioid analgesia

Hypogonadism is present in 75% of male and 21% of female patients taking opioid analgesia for chronic pain. The prevalence of adrenal insufficiency has not been similarly assessed, but it is estimated to affect 15% of patients receiving chronic intrathecal opioid treatment.

Gibb *et al.* performed a cross-sectional study on patients attending chronic pain clinics who had received opioid analgesics for at least 6 months. An 08.00 cortisol measurement, a short synacthen test and the SF-36 health questionnaire were used to assess 48 patients. Four had a basal morning plasma cortisol <10nmol/l,

and three of these failed to mount an adequate response to synacthen. Lower basal cortisol was also associated with lower quality of life scores.

It is acknowledged that chronic pain itself is a confounding factor in this scenario, since it has been associated with a disrupted circadian rhythm and low morning cortisol. It is not clear whether patients with mild opioid-related adrenal insufficiency benefit from glucocorticoid treatment, but measuring early morning plasma cortisol in those receiving long term, high dose opioid analgesia is suggested. It is conceivable that, during acute illness, such patients may be at risk of hypoadrenal crisis.

Read the full article in *Clinical Endocrinology* **85** 831–835

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Hyponatraemia in nivolumab-induced adrenal failure

Checkpoint inhibitors are used increasingly in the management of patients with advanced malignant melanoma. These drugs are associated with immune-related adverse events affecting dermatological, gastrointestinal, hepatic, endocrine and other systems. Endocrine complications such as hypophysitis, hypopituitarism and autoimmune thyroiditis are well recognised.

Trainer *et al.* describe the first case of nivolumab-induced adrenalitis and primary adrenal failure presenting with hyponatraemia in a 43-year-old man with malignant melanoma. The failure of the hyponatraemia to fully resolve with hydrocortisone monotherapy, unremarkable pituitary magnetic resonance

imaging, bilateral increased activity on FDG-PET/CT (¹⁸F-fluorodeoxyglucose-positron emission tomography/computed tomography) and elevated adrenocorticotrophin and renin levels were consistent with aldosterone deficiency and primary adrenal failure. Serum sodium and plasma renin returned to normal with the addition of fludrocortisone.

The case highlights a potentially life-threatening complication of checkpoint inhibitors and the need for patient education and clinician awareness.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* **11** EDM160108

ENDOCRINE CONNECTIONS

Bromocriptine and insulin sensitivity in lean and obese subjects

The US Food and Drug Administration has approved bromocriptine for use in type 2 diabetes, although its glucose-lowering mechanism is unclear. Bahler *et al.* observed that lean, healthy patients actually became less insulin-sensitive following 2 weeks of bromocriptine treatment. They set out to determine the drug's mechanism, and how this varies in lean versus obese subjects, and with time of administration.

They recruited 16 male Caucasian subjects (18–35 years): 8 obese (body mass index (BMI) >27kg/m²) and 8 lean (BMI 19–23kg/m²). All received bromocriptine for 2 weeks in the morning, and 2 weeks in the evening, at a dose of 1.25mg daily, titrating up to 2.5mg in the second week.

Oral glucose tolerance tests were performed before and after each 2-week treatment, along with an assessment of energy expenditure. Bromocriptine increased insulin sensitivity in obese subjects, but only did so in the lean subjects when administered in the evening.

The greater effect in obese subjects may be related to a lower dopamine binding capacity, induced by obesity-related conformational changes in the D2 receptor, while in lean subjects the diurnal variation in dopamine levels may be more significant.

Read the full article in *Endocrine Connections* **5** 44–52

Novel hormone explains how we get fat

Obesity is a major public health concern, and individuals who are overweight face serious risks to their health. However, the molecular mechanisms by which excessive production of adipocytes is initiated in an individual have remained largely elusive.

Through studies on both mice and humans, Wong *et al.* have identified a novel hormone called ADAMTS1, which controls the first step in the differentiation and maturation of fat cells. Lower levels of ADAMTS1 are associated with increased adipogenesis. ADAMTS1 is produced by adipocytes, but the team have shown that its rate of production is affected by external factors including high fat diets and glucocorticoid exposure.

Although there is still much to discover about the activity and regulation of ADAMTS1, this study suggests intriguing future approaches that might lead to medical interventions for targeting the obesity epidemic.

Read the full article in *Science Signaling* **9** ra103

Individualised vitamin D supplementation in pregnancy

Vitamin D deficiency is common in pregnant women, causing harm to maternal well-being, fetal development and the child's long term skeletal health. Although a standardised vitamin D supplement is recommended during pregnancy, many factors can affect how much such supplements translate into a raised maternal vitamin D level.

Moon *et al.* studied 829 pregnant women from 14 weeks of gestation. Half were given a dose of 1000IU cholecalciferol per day, while the remainder received a placebo. The supplement had a significant positive effect in raising maternal vitamin D. However, in the group given vitamin D, factors associated with a lower level of maternal vitamin D at 34 weeks included higher pregnancy weight gain, lower compliance in taking the supplement, lower early pregnancy vitamin D levels and giving birth in the winter (as opposed to the summer).

The findings suggest that the exact levels of vitamin D supplementation recommended for pregnant women should be tailored to an individual's circumstances, such as anticipated season of delivery.

Read the full article in *Journal of Clinical Endocrinology & Metabolism* doi:10.1210/jc.2016-2869

Role reversal: sex hormones in the meerkat

Differences in reproductive hormone concentrations between the sexes are the norm in vertebrates, with males typically exhibiting an androgen bias and females an oestrogen bias. Although these differences can be reduced in female-dominant species, typically the most dominant females still exhibit lower androgen profiles than males.

Davies *et al.* measured sex hormone concentrations in the meerkat (*Suricata suricatta*), an aggressively dominant co-operative breeder, where the alpha females produce over 80% of pups that survive until adulthood. They found unusual hormone patterns in both sexes, with males exhibiting high oestrogen levels (relative to subordinate females) and females having higher androstenedione levels and equivalent testosterone levels when compared with males. While hormone profiles did not significantly differ between males, more dominant females exhibited significantly higher androgen levels than their subordinate counterparts.

This is the first example in vertebrates of such an unusual reproductive hormone balance between the sexes. Higher levels of androgens in the female may underlie natural history traits of female aggression and reproductive skew exhibited by this species.

Read the full article in *Scientific Reports* **6** 35492



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SHEDDING LIGHT ON SLEEP AND AROUSAL

WRITTEN BY STUART N PEIRSON, VIOLETTA PILORZ & RUSSELL G FOSTER



We spend around a third of our lives asleep. Sleep disruption is a major contributing factor to health problems ranging from poor vigilance and memory, reduced reaction times, reduced motivation, depression, metabolic abnormalities and obesity to impaired immune function and elevated risks of cancer and coronary heart disease.

The sleep/wakefulness cycle is a complex process, involving multiple areas of the brain and all the key neurotransmitters. These complex neural networks are regulated by 'sleep pressure', the familiar process whereby being awake gives rise to an increased requirement for sleep (also called the sleep homeostat), as well as a drive for wakefulness produced by the body's internal 24-h (circadian) clock.

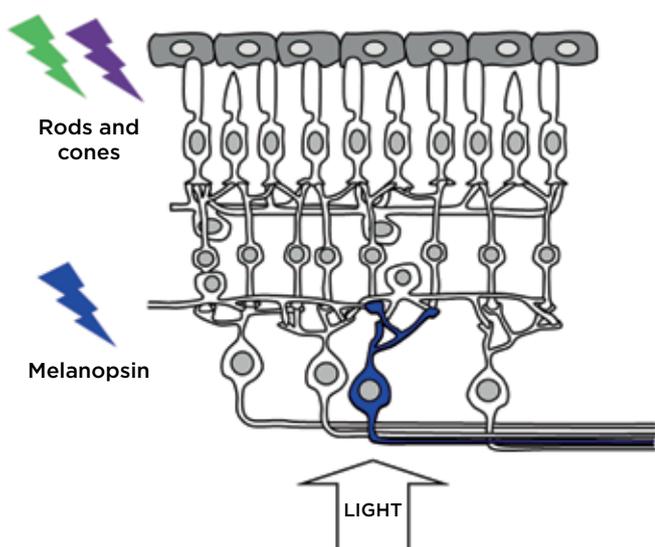
NOVEL PHOTORECEPTORS

Light exerts profound effects upon our physiology and behaviour. The familiar function of the eye is as an image detector, but the eye also detects environmental irradiance for the regulation of the circadian system (entrainment), sleep propensity and levels of alertness.

The photoreceptors mediating vision are the rods and cones, whilst irradiance is measured by a subset of photosensitive retinal ganglion cells (pRGCs), which express the blue light-sensitive photopigment melanopsin (Figure 1). Significantly, pRGCs also receive inputs from the rods and cones, which alter their endogenous photosensitivity.

We now appreciate that the eye performs two very different sensory tasks – it generates a visual image of the world and samples the gross changes in the light environment to drive responses including entrainment and the regulation of sleep.

Figure 1. Retinal photoreceptors: in addition to the rod and cone photoreceptors which mediate vision, a subset of photosensitive retinal ganglion cells (pRGCs) express the photopigment melanopsin and are critically important in the regulation of a wide range of non-image-forming responses to light. S.Peirson



SLEEP OR AROUSAL?

Previous studies have shown that mice lacking melanopsin show impaired sleep induction in response to white light. However, other studies have shown that light increases glucocorticoid release – a response typically associated with stress and increased arousal, and incompatible with sleep.

To address these contradictory findings, we studied the responses of mice to light of different wavelengths (colours). Given the previous data on the role of melanopsin in the regulation of sleep, we predicted that blue wavelength light would be the most effective at inducing sleep. Surprisingly, we found that blue light inhibited sleep induction, whilst green light resulted in rapid sleep onset! An explanation for these findings comes from the opposing effects of different wavelengths of light on two different neural pathways.

Melanopsin-expressing pRGCs signal to the master circadian clock in the suprachiasmatic nucleus (SCN) as well as the sleep switch in the ventrolateral preoptic area (VLPO). In addition, projections from the SCN also directly regulate the sympathetic nervous system, leading to behavioural arousal and elevated adrenal corticosterone levels.

This arousal response to light is attenuated in mice lacking melanopsin – these animals go to sleep more quickly in response to blue light. However, the rapid sleep induction seen in response to green light is attenuated in melanopsin-deficient mice. How can these unexpected results be explained?

'The eye generates a visual image of the world and samples the gross changes in the light environment to drive responses including entrainment and the regulation of sleep.'

INTEGRATING ROD, CONE AND MELANOPSIN SIGNALS

The melanopsin-expressing pRGCs are not all the same, and various subtypes have been identified, termed M1–M5. M1 cells express the highest levels of melanopsin, are strongly light-sensitive and are less dependent on input from rods and cones. M2–M5 cells, however, are more dependent on input from rods and cones.

Significantly, the light input to the SCN, which stimulates arousal, is thought to be largely driven by M1 cells, which, because of their dependence upon melanopsin, are predominantly blue-light sensitive. By contrast, the sleep-promoting signal to the VLPO appears to be derived from M2–M5 cells which, because of their strong rod/cone inputs, are effectively more green-sensitive. Such conclusions are supported by findings showing that cells in the SCN are more strongly stimulated by blue light, whilst the cells of the VLPO show stronger responses to green light (Figure 2).

But why do mice lacking melanopsin show impaired responses to green light? An explanation comes from recent data showing that melanopsin also appears to play a role in the light adaptation of rod and cone pathways.

Adaptation is the ability of the visual system to adjust its sensitivity to the background light level, so that objects can be detected against background

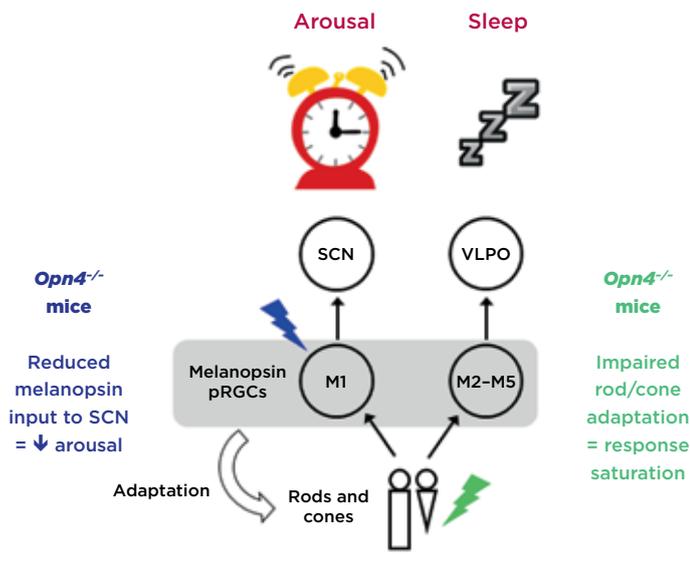


Figure 2. Model illustrating the opposing effects of light on sleep and arousal. M1 photosensitive retinal ganglion cells (pRGCs) express high levels of melanopsin and respond maximally to blue light. These cells project directly to the suprachiasmatic nucleus (SCN) and promote arousal via SCN inputs to the sympathetic nervous system. By contrast, M2-M5 cells are more dependent upon rod and cone input, and are thus more sensitive to green light. These cells project to the sleep switch in the ventrolateral preoptic area (VLPO). Mice lacking melanopsin (*Opn4*^{-/-}) show impaired arousal responses to blue light. Furthermore, as melanopsin contributes to light adaptation of rods and cones, mice lacking melanopsin also show impaired responses to green light due to response saturation. S.Peirson

under both very low light levels (dark adaptation) and very bright light (light adaptation). The retina accomplishes this by switching from rod- to cone-based vision as light levels increase, as well as by cellular changes in photoreceptor sensitivity. Furthermore, changes in retinal circuits also occur, and central to this task is the ability to accurately measure ambient light levels.

Melanopsin plays a key role in light adaptation, acting as a light meter to adjust the sensitivity of the retina. As such, mice lacking melanopsin show impaired light adaptation under bright light, saturating more quickly, and resulting in impaired responses under green light.

CONCLUSIONS

These data show that different wavelengths of light can promote either sleep (green light) or arousal (blue light) in mice, and demonstrate that the regulation of sleep in response to light is considerably more complex than originally conceived.

Clearly, translating these discoveries in mice to a diurnal species such as humans is complex, but the findings presented here will provide a platform to develop experimental protocols in order to understand how the different photoreceptors of the eye drive sleep and arousal in humans.

Such knowledge will be critical if we are to understand how inappropriately timed exposure to artificial lighting, such as blue-enriched LED light from mobile devices such as laptops, tablets and smartphones, will or will not disrupt sleep.

STUART N PEIRSON, VIOLETTA PILORZ & RUSSELL G FOSTER
 Sleep and Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford

UNPICKING GnRH SIGNALLING DYNAMICS: MATHEMATICAL APPROACHES

WRITTEN BY KATHRYN GARNER & CRAIG McARDLE



Gonadotrophin-releasing hormone (GnRH) is a peptide hormone that is secreted from the hypothalamus in pulses to control reproduction. It does this via GnRH receptors (GnRH-Rs) on pituitary gonadotrophs that mediate its effects on the synthesis and secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH).

The stimulation paradigm is crucial, since pulsatile and sustained GnRH have very different effects on the target cells, and this phenomenon is exploited in therapeutic manipulation of the system.¹ Understanding how the complex inputs are sensed and processed by gonadotrophs forms the core of our research, and has led us to use mathematical approaches to enrich our wet-lab data.

EARLY INSIGHTS INTO GnRH

The structural determination and synthesis of GnRH were landmarks in the development of the field of neuroendocrinology (for which the Nobel Prize was awarded in 1977). They were rapidly followed by attempts to understand its mechanism of action. In the early days, all that was really known was that GnRH acted via receptors to increase production of second messengers.

At the time, the logic of cell signalling was very simple: hypothesising that A→B→C, one would set to work with pharmacological inhibitors and mimics to prove or disprove the hypothesis. However, the original signalling pathway idea has given way to the notion that GnRH (like other extracellular signals) engages a complex signalling network with numerous sites of divergence and convergence, as well as routes for positive and negative feedback. We now work with increasingly complex network cartoons for the GnRH signalling architecture, yet these are still vast over-simplifications, not least because they largely ignore dynamics.

MATHEMATICAL REASONING

Several years ago, Craig was discussing how such a network might decode input dynamics with Krasimira Tsaneva-Atanasova, a colleague in mathematical engineering. On seeing our latest network topology model, she pointed out that it was far too complex to understand by ‘intuition’ alone.

She outlined a mechanistic modelling approach. We then set about developing a model for GnRH signalling based on a series of ordinary differential equations (ODEs) describing receptor occupancy through to G-protein-mediated activation of phospholipase C, calcium mobilisation, activation of the calcium-sensitive transcription factor NFAT (nuclear factor of activated T cells) and protein kinase C-mediated activation of ERK (extracellular signal-regulated kinase).

We included only molecules that have actually been shown to be necessary for GnRH action *in vivo* (GnRH, GnRH-R, ERK, gonadotrophin α -subunit, LH β and FSH β), with the addition of a calcium effector. Moreover, since ERK2-GFP (green fluorescent protein) and NFAT-EFP (emerald fluorescent protein) reporters both translocate from the cytoplasm to the nucleus on activation, we were able to use these as live cell read-outs for GnRH signalling during trains of GnRH pulses.^{2,3}

Leaning heavily on previous GnRH signalling models, together with models for ERK activation, calcium mobilisation and NFAT activation, we developed a mechanistic model that was trained on and validated against our wet-lab data. This model has gone through multiple iterations. The earliest did not include GnRH-R trafficking and was trained on data for GnRH-R signalling in a HeLa cell model,⁴ whereas the latest incorporates GnRH-R internalisation and recycling and is trained against wet-lab data for signalling of endogenous GnRH-R in a gonadotroph-derived cell line.⁵

ENHANCED PREDICTIONS

It might seem that we are merely generating a mathematical description of what we’ve already seen in our wet-lab data. However, our modelling offers an entrée into a virtuous cycle in which a model trained against wet-lab data is used to create predictions that lead to wet-lab tests yielding data that can be used to improve the model, so that the improved model can be used for further predictions.

Wet-lab experiments with pulsatile GnRH are very labour intensive. Ideally, we’d like to vary pulse frequency, width and concentration in parallel, and this is straightforward *in silico*, but not practical *in vitro*. Instead, we use simulations to explore possible system behaviours and help us plan experiments to reveal actual behaviours.

ANSWERING QUESTIONS

In a recent study, we used a minimal model to address the fundamental question of why GnRH secretion is pulsatile. We found that the use of a pulsatile input could increase efficiency, generate specificity and make the system resistant to receptor trafficking.⁵ We also asked whether upstream negative feedback (i.e. receptor internalisation) could explain why maximal responses to GnRH are very often obtained with sub-maximal GnRH pulse frequencies. The simulations revealed that it could, but only under conditions where receptor internalisation rates are high and desensitisation of downstream responses are marked, neither of which are consistent with wet-lab data. Consequently, our current emphasis is on downstream (i.e. transcriptional) mechanisms that could achieve this.

Notably, our ODE approach models a single cell, yet in our wet-lab data we observe enormous cell-cell variability in signalling responses. We have addressed this by applying a statistical measure known as mutual information, originally developed to analyse electronic communications, to quantify the information transferred along our noisy signalling pathways.

In another recent study, we used this approach to consider the effects of negative feedback on sensing of GnRH, focusing on ERK-dependent feedback (rapid transcription-independent and slow transcription-dependent feedback) and on receptor desensitisation, finding that downstream adaptive ERK-mediated feedback fine-tunes hormone sensing, with optimal GnRH sensing at intermediate feedback intensities.⁶

Indeed, it is clear that we were unable to fully comprehend the GnRH network topology using

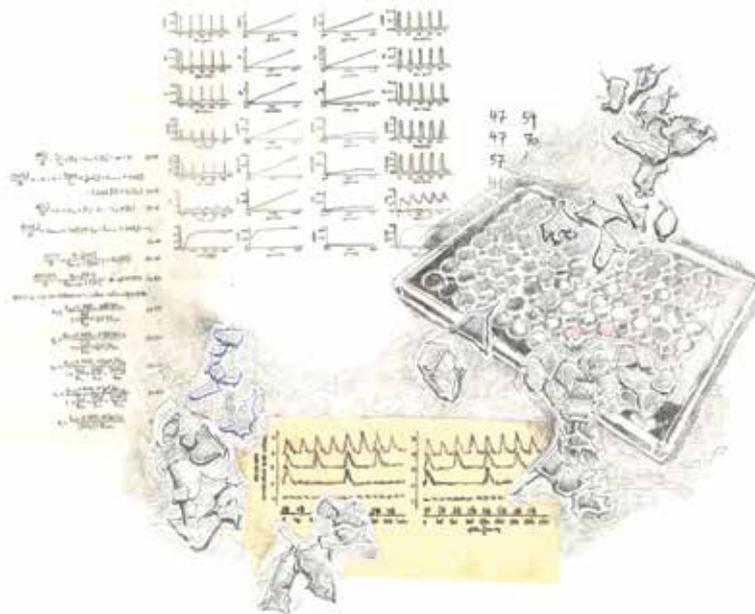
our intuition alone. Beginning with mechanistic modelling, we have begun to unravel the complexities of pulsatile GnRH signalling and now consider the contribution of individual cells to the variability within a whole cell population.

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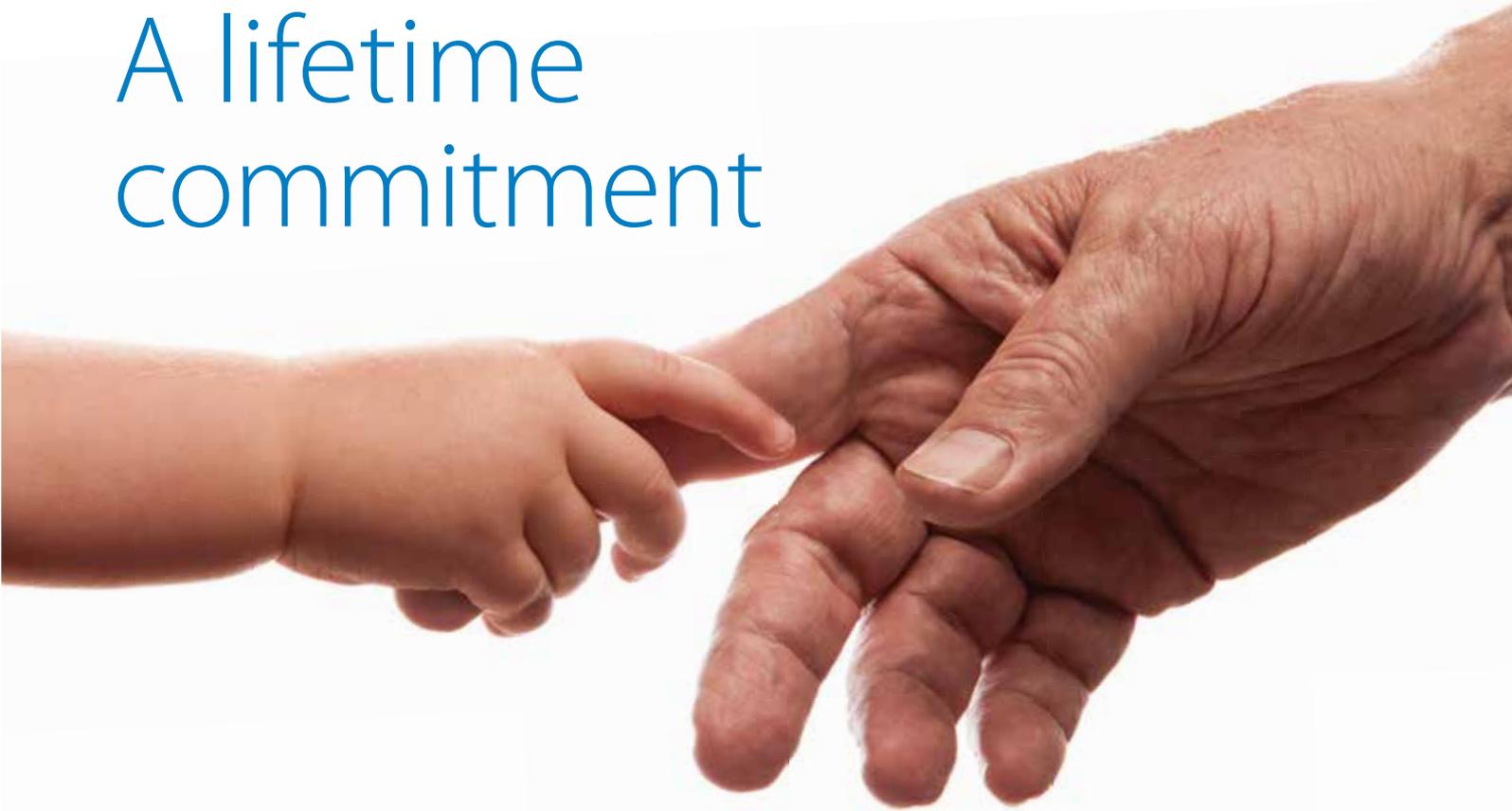
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A virtuous cycle in which a model trained against wet-lab data (top) is used to create predictions that lead to wet-lab tests (right) yielding data (bottom) that can be used to improve the model (left). Illustration by Kathryn Garner

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NOT JUST SKIN DEEP: MONOCLONAL THERAPIES AND PITUITARY ENDOCRINOPATHY

WRITTEN BY ANDREW S POWLSON & CARLA MORAN



Primum non nocere or 'first do no harm' is a central tenet of medicine, and one to which physicians have aspired for millennia. In practice, physicians have been required to weigh the therapeutic benefit of an agent or intervention against its potentially harmful sequelae: a 'risk assessment' mandated, though with variable adherence, from the ages of blood-letting, leeches and elemental therapies through to the present day.

Of course, the more devastating and refractory to conventional therapies the disease is, the lower the threshold for acceptance of side effects. A therapeutic agent with foreseeable side effects may be more safely and efficaciously used with due vigilance and multi-disciplinary liaison. In some cases, that will mean different specialties working with us, as endocrinologists.

IMMUNOTHERAPY AND THE MEDICAL ONCOLOGIST

One therapeutic avenue which has become interdisciplinary is the use of immunomodulating agents which, in the simplest terms, involves modifying host immunity to target a disease process.

One of the earliest uses of humanised monoclonal antibodies to such an end came with the administration of alemtuzumab in the treatment of multiple sclerosis. Our experience of this alerts us to the potential for immunomodulation to result in an increased incidence of autoimmune disease against endocrine organs. Immune-mediated thyroid dysfunction is an important side effect of alemtuzumab therapy (occurring in 40% of patients treated at our institution). As such, both neurologists and endocrinologists recognise the need for vigilance and monitoring of thyroid function in individuals treated with this agent.

More recently, monoclonal antibody therapy has entered oncological practice, with the development of agents directed against immune checkpoint molecules such as CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) or PD-1 (programmed cell death protein 1). Inhibition of these immunological 'checkpoints' modulates the T cell response to malignancy, enhancing the activity and proliferation of T cells and thus inhibiting tumour cell proliferation and survival.

Use of these agents is having a dramatic effect on the treatment of advanced melanoma, where untreated median survival is 8–10 months. The agents are now being explored for use in other malignancies.

Conversely, of course, such promotion of the T cell response can affect self-tolerance, in turn promoting development of autoimmune responses to native tissues, resulting in immune-related adverse events (IRAEs), including endocrinopathies.

IPILIMUMAB

Ipilimumab (Yervoy®, Bristol Myers-Squibb) was approved for use by the US Food and Drug Administration in metastatic or unresectable melanoma in 2011. It was the first drug to prolong the lives of patients with advanced disease.

This humanised monoclonal antibody targets the immune checkpoint antigen CTLA-4 and it has become increasingly clear that IRAEs are common with this agent. These include dermatological and gastrointestinal manifestations as well as the development of autoimmune endocrinopathies:

Table. Illustrative presentation of ipilimumab-induced hypophysitis: a 77-year-old man with metastatic melanoma had received two cycles of ipilimumab (commencing 2 months previously) before being admitted with lethargy, fatigue, dizziness, nausea and vomiting. He was markedly hyponatraemic with pan-anterior hypopituitarism.

Parameter	Results	Reference range
Sodium	122	133–146mmol/l
Adrenocorticotrophin	<5	0–50ng/l
Cortisol at 9am (unstimulated)	<25	280–650nmol/l
Cortisol (30min post-Synacthen*)	33	>450nmol/l
Thyrotrophin	0.38	0.35–5.5mU/l
Free thyroxine	3.4	10–19.8pmol/l
Free tri-iodothyronine	2.0	3.5–6.5pmol/l
Luteinising hormone	2.2	1.5–6.3U/l
Follicle-stimulating hormone	1.5	1.0–10.1U/l
Testosterone	0.2	8–29nmol/l
Prolactin	6	45–375mU/l
Insulin-like growth factor-1	5.2	10–25nmol/l

most commonly hypophysitis, but also primary adrenal insufficiency and thyroid disease.

The extent of the issue has become increasingly apparent in recent years, as will have been evident to those attending endocrine meetings, where a veritable glut of case reports has appeared. A number of recent reviews consider the phenomenon in detail.^{1,2}

The pathogenesis of ipilimumab-induced hypophysitis is unclear and no histological specimen from such a case has been reported, but the phenomenon is perhaps not unexpected. *CTLA4* polymorphisms are associated with autoimmune endocrinopathies such as Graves' disease and Hashimoto's thyroiditis; the antigen is expressed on both mouse and human anterior pituitary cells and focal infiltration of macrophages and lymphocytes has been demonstrated in pituitary glands of anti-CTLA-4 treated mice.³

IPILIMUMAB-INDUCED HYPOPHYSITIS

Clinical features

The reported prevalence of hypophysitis in ipilimumab-treated patients varies by study (0–17%). It seems that earlier studies may well have under-reported its existence, in part because of a lack of awareness and inconsistent monitoring and reporting measures. In turn, this may also reflect the ambiguity of the symptomatology of hypopituitarism, with headaches the most common presenting feature, along with other non-specific features of anterior hypopituitarism such as nausea, vomiting, weight loss, lethargy and confusion. Hyponatraemia may be evident; diabetes insipidus and visual compromise have been reported only rarely.

Unlike idiopathic hypophysitis, which tends to predominate in females of reproductive age, ipilimumab-induced hypophysitis appears to have both male sex and age as risk factors. A dose effect is also present. Hypogonadotrophic hypogonadism, and secondary thyroid and adrenal insufficiency, are most common, with the growth hormone axis more rarely involved. This last observation may be due to limited assessment of the growth hormone axis in many studies.

Presentation occurs most commonly at 2–3 months post-initiation (mean 9 weeks), though delayed presentation has been reported. This tends to be later than for other IRAEs, such as gastrointestinal effects. Notably, some pituitary function may recover; up to 50% of patients regain thyrotrophin and gonadotrophin secretion in some series. In contrast, hypothalamic-pituitary-adrenal axis recovery is rare, and several authors report persistent hypopituitarism. It is not clear how often and how robustly patients described in many studies were assessed for recovery of hypopituitarism.

Radiology

Pituitary imaging may demonstrate a marginally increased anterior pituitary volume (mean increase 5mm) and/or heterogeneity of contrast enhancement. This appearance can precede the development of anterior hypopituitarism and may only be transiently evident, with all patients in one series showing reduction of radiological features after 40 days. The typical mild global enlargement may explain the lack of visual pathology in these patients.

Management

Awareness of the potential for hypophysitis and its likely symptoms, and recognition of these should they manifest, are both key. This is perhaps where close liaison and mutual education between oncologists and the endocrine team are particularly important.

Early advice suggested measuring thyroid function before commencement and before each subsequent dose. A more structured anterior pituitary and electrolyte profile before starting ipilimumab as a baseline would seem

prudent, along with continuous assessment for clinical features and further anterior pituitary testing at intervals during and after the course of treatment. The possibility of late clinical presentation should be kept in mind.

Pituitary imaging should be considered if symptoms or biochemistry dictate. Once present, adrenal, and subsequently thyroid, insufficiency should be treated with physiological replacement doses. There is no clear evidence that supraphysiological (immunosuppressive) doses of glucocorticoid alter the recovery rate of endocrinopathies or resolve pituitary enlargement,⁴ though such doses are often prescribed and may be advised if, for example, there is a mass effect on magnetic resonance imaging (MRI).

Early papers suggested permanent discontinuation of ipilimumab in all cases, but more recently authors have suggested that it may be reintroduced after a delay once appropriate hormone replacement has been commenced.

Discussion between oncology and endocrinology is advised. An ongoing need for hormone replacement, and thus endocrine follow-up, is to be expected. Possible permanent hypopituitarism must be weighed against the potential life-extending benefits of ipilimumab. Indeed, it has been suggested that patients who develop hypophysitis, and thus have a greater immune response, may have a survival advantage.

OTHER MONOCLONAL THERAPIES IN ONCOLOGY

Ipilimumab was just the first in a line of promising immune checkpoint modulators. More recent examples include monoclonal antibodies targeting PD-1, such as nivolumab and pembrolizumab. It has recently been suggested that these agents have an improved survival benefit over ipilimumab in advanced melanoma, and IRAEs seem to be less frequent and less severe. Hypophysitis is rarer with these agents (<1%), but thyroid disease is common (up to 9%) and may occur as transient thyrotoxicosis, thyroiditis or primary hypothyroidism.

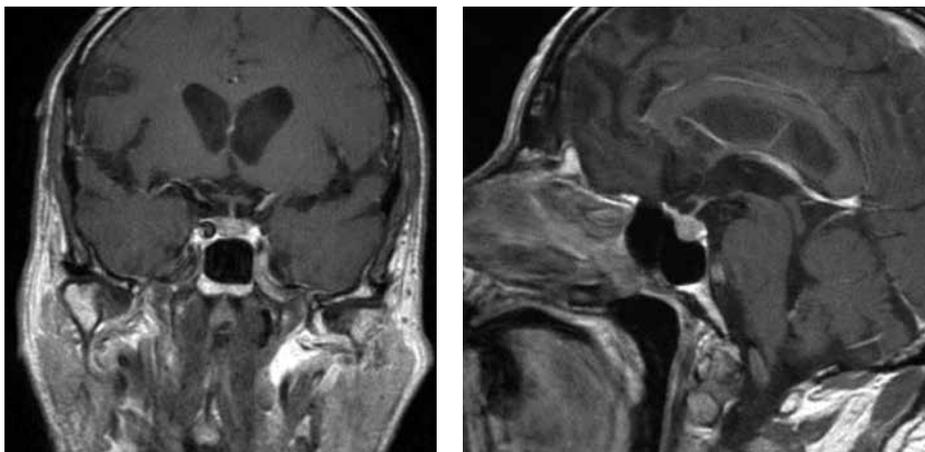
Notably, combining anti-CTLA-4 and anti-PD-1 agents increases the risk of IRAEs, resulting in thyroid dysfunction in up to 22% of cases.

In summary, the efficacy of checkpoint modulating immunotherapies in treatment of advanced melanoma is resulting in their increasing use, and hence the prevalence of immune-related endocrinopathy is likely to rise.

Currently, prospective studies and accurate data on recovery of endocrine dysfunction are lacking. Liaison between endocrinologists and oncologists is required to increase our understanding of the pathogenesis and course of these phenomena and to standardise care pathways.

‘Of course, such promotion of the T cell response can affect self-tolerance, in turn promoting development of autoimmune responses to native tissues, resulting in immune-related adverse events, including endocrinopathies.’

Figure. T1-weighted MRI with gadolinium in the same patient as described in the Table demonstrated a modest diffuse enlargement of the pituitary gland for his age, with some heterogeneity of contrast enhancement across the gland, consistent with hypophysitis.



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ENDOCRINOLOGISTS AND THE CONSEQUENCES OF CANCER TREATMENT

WRITTEN BY HELEN SIMPSON



Between 30 and 50% of us will have a cancer diagnosis during our lifetime and, increasingly, cancer is becoming a long term condition. In the UK, 2.5 million people live with and beyond cancer.

Of these, it is estimated that 625,000 have a health problem or disability as a result of cancer and its treatment. This can be highlighted most clearly in data from survivors of childhood cancer. There is now an 80% 5-year survival rate. These data highlight the great steps taken in achieving a cure: we can now expect good outcomes, and success. However, there is a downside. By the age of 50, survivors have a cumulative incidence of significant/fatal health conditions of some 53%: this is more than double the incidence in matched sibling controls.¹

For example, in female survivors of haematopoietic stem cell transplant 10 years after treatment, over 80% have premature ovarian insufficiency. There is also a two- to fourfold increase in cardiovascular disease, and significant rates of dyslipidaemia, hypertension and diabetes.

A ROLE FOR ENDOCRINOLOGISTS

So what has this got to do with endocrinology? Quite a lot, in fact. For me, as always, it started with my patients. To look after them as well as possible, I needed to understand the details and consequences of their cancer treatments. If we consider the multiple types of cancer treatment used, we can easily see that there is a large impact on the endocrine system.

Two of the 'big' cancers, breast and prostate cancer, include hormone therapies rendering patients hypogonadal. This often leads to symptoms that are difficult to manage and an increased risk of osteoporosis. Radiotherapy for head and neck cancers causes hypopituitarism. Chemotherapy, in particular alkylating agents, can cause hypogonadism. Newer biological agents (in particular immune checkpoint inhibitors) can cause hypophysitis and thyroiditis.

Importantly, as endocrinologists, we often take on a significant role in delivering general medicine in our hospitals. We may therefore encounter patients with heart failure as a result of chemotherapy (anthracyclines), fractures as a result of pelvic irradiation, or patients sadly presenting with a second malignancy as a consequence of their initial cancer treatment. In my clinics, I manage survivors of childhood malignancies, in particular those of the head and neck, and haematological malignancies, as well as caring for patients with endocrine malignancies and neuroendocrine tumours. However, I increasingly encounter cancer survivors of all types.

CURRENT PROVISION OF CARE

Services handling consequences of cancer treatment, or late effects, are currently not widely established within the NHS. The most robust systems are in place for survivors of haematological malignancies, in particular

haematopoietic transplants. Otherwise, long term care is inconsistent or not available.

Even where services are present, there remain obstacles to optimal care. Whilst survivors of childhood malignancies often have a cancer treatment summary which lists the types and dose of chemotherapy and radiotherapy that were administered, too often this is not available for adult survivors. This is particularly the case if treatment took place several years previously, in a different institution or a different region.

The apparent care gap is not in service delivery alone. Many physicians are not aware of the impact of cancer treatments on long term health, and the consequences of cancer treatment are not covered widely in undergraduate or postgraduate curricula.

ANTICIPATION MATTERS

So, while we can now expect good outcomes in much of the cancer we deal with, with this comes a need to anticipate managing the consequences of the disease and its treatment. One cannot go without the other.

What can we do as endocrinologists to improve the experience and outcome for our patients? The answer is to 'start simple' and ask:

1. Does this patient have a cancer diagnosis?
2. What type of cancer?
3. What treatment did they have?

IN SEARCH OF GUIDANCE

Along with others, I am currently compiling guidance on the endocrine consequences of cancer treatment, with recommendations on what we should be doing for our patients. These will be published in *Clinical Endocrinology* and will also be available on the Society for Endocrinology and Macmillan websites initially.

Colleagues in cardiology and gastroenterology are ahead of the curve, and have already published guidance and patient information resources.^{2,3} We are also working with Macmillan to produce endocrinology guidance for GPs and patient information. This is an exciting opportunity to reach out to millions of cancer survivors and their healthcare professionals.

Ultimately, all cancer patients should have treatment summaries and access to surveillance/management pathways across primary, secondary and tertiary care. Electronic processes should be available to ensure all healthcare professionals can access appropriate clinical guidance when they come across cancer survivors in their clinical practice. Models of care need to be developed locally: these should break down boundaries between primary, secondary and tertiary services and also work across specialties within hospitals.

But we need an important reality check: all this needs to be achieved in a healthcare environment of increasing demand and decreasing financial resources.

Before we all get overwhelmed with a sense of impending doom, we can all make small steps in our own practice. As a starter, how about, 'Think cancer ... and think consequences of cancer treatment'?

HELEN SIMPSON

Cambridge University Hospital NHS Foundation Trust



Pop legends Kylie and Nile Rodgers are both cancer survivors. Shutterstock (Kylie); Wikimedia Commons/Joe Mabel (Nile)



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ENDOCRINE THERAPY FOR BREAST CANCER: A RENAISSANCE

WRITTEN BY NEIL PORTMAN, SARA WAHLROOS, ANDREW PARKER, DAVENDRA SEGARA & ELGENE LIM



Endocrine therapy for hormone receptor (HR)-positive breast cancer has been an incredible success story, drastically reducing the rate of disease recurrence. Around 70% of breast cancers are HR-positive and express the oestrogen receptor (ER), a ligand-dependant transcription factor that transduces oestrogen signalling to pro-survival transcriptional programmes.

In this cancer subtype, the ER is the driver of cell growth and is the target for systemic endocrine treatment in both adjuvant and metastatic settings.¹ Inhibition of ER signalling may be achieved by the following means:

- removal of the circulating ligand by blocking oestradiol biosynthesis with aromatase inhibitors (AIs) and luteinising hormone-releasing hormone agonists
- inactivation of ERs by antagonising oestrogen binding using selective ER modulators, such as tamoxifen
- down-regulation of ERs using selective ER degraders (SERDs), such as fulvestrant.

Five years of adjuvant endocrine therapy reduces the relative breast cancer recurrence and mortality rates by about 50 and 33% respectively, and has a prolonged carry-over effect on mortality throughout the first 15 years.² However, HR-positive breast cancers have a long natural history, and approximately equal proportions of patients with early stage breast cancer treated with 5 years of tamoxifen will relapse between 0–5 and 5–14 years from diagnosis.²

To reduce the incidence of late recurrences, multiple trials have shown that disease-free survival benefits from extending adjuvant endocrine therapy to 10 years.^{1,3,4} Unfortunately, the absolute benefit of extended therapy is small, and comes at the cost of therapy-associated morbidity, including an increased risk of uterine cancer and thromboembolic disease with tamoxifen, and osteoporosis and fractures with AIs. There is a clear need for better adjuvant strategies than merely extending the duration of endocrine therapy.

'The therapeutic repertoire in the management of our patients has never been as diverse as it is today.'

TACKLING THE PROBLEM OF RESISTANCE

Endocrine therapies target either the ligand or the transcription factor, and resistance to these therapies can be acquired by dispensing with ligand dependence or with reliance on ER-driven transcription.

Genetic approaches

Activating mutations of the *ESR1* gene (which encodes ER) can confer ligand independence and have been reported in cell-free DNA (cfDNA) of 39% of patients with metastatic, endocrine-resistant disease.⁵ The presence of *ESR1* mutations is associated with poorer outcomes and resistance to further AI therapy.⁵ However, tumours harbouring *ESR1* mutations are relatively more

sensitive to alternative endocrine therapies such as SERDs, which degrade the ER protein, rather than the oestrogen/ER interaction.

ER signalling is regulated epigenetically, and it has recently been shown that epigenetic methylation (switching off) of ER-responsive enhancer elements is associated with reduced expression of key regulators of ER action and the development of resistance.⁶ Etinostat, a histone deacetylase inhibitor that acts by reversing epigenetic transcriptional silencing, has been granted breakthrough therapy designation by the US Food and Drug Administration (FDA) in combination with the AI exemestane, based on promising phase II results from the Encore 301 study.⁷

Targeting signalling pathways

The upregulation of alternative proliferative signalling pathways provides another mechanism of endocrine resistance.⁸ The two main pathways currently gaining clinical attention are the PI3K/Akt/mTOR pathway and the cyclin dependent kinase (CDK)/cyclin axis.

The PI3K pathway is activated by multiple stimuli and transduces growth and survival signals. Hyperactivation of this pathway is common in endocrine-resistant breast cancer,⁹ and can result from epigenetic dysregulation of the pathway, aberrant activation of upstream signalling factors or activating mutation of key pathway components. Several PI3K pathway-targeting drugs are currently in phase III clinical trials, and the mTOR inhibitor everolimus has been approved by the FDA in combination with exemestane for patients that have progressed on prior AI therapy. The pivotal phase III BOLERO 2 trial demonstrated an improvement in median progression-free survival (PFS) from 3.2 months (exemestane) to 7.8 months (exemestane plus everolimus).¹⁰

Cyclin D transcription is a key ER proliferative target which controls cell cycle progression from G1 to S phase via activation of CDK4/6. ER-independent expression and stabilisation of cyclin D is linked to acquisition of endocrine resistance, and blocking the action of CDK4/6 can resensitise endocrine-resistant cancer cells to endocrine therapy. The CDK4/6 inhibitor palbociclib has recently been approved for use in metastatic breast cancer in combination with an AI by the FDA.

The phase III PALOMA 3 study in patients who progressed on prior AI therapy demonstrated an improvement in median PFS from 3.8 months (fulvestrant) to 9.2 months (fulvestrant plus palbociclib).¹¹ In the first-line metastatic setting, the phase III PALOMA 2 trial reported an increase of median PFS from 14.5 months (AI letrozole) to 24.8 months (letrozole plus palbociclib),¹² which is the longest duration of any therapeutic strategy in metastatic ER-positive breast cancer to date. This combination strategy was effective in patients with cfDNA that were either *ESR1* wild type or mutant.⁵

LOOKING TO THE FUTURE

Combination therapeutic strategies with an endocrine backbone that have significantly improved outcomes in the metastatic setting are now being employed in the adjuvant setting, particularly in patients with higher risk disease.

Above Breast cancer cells. Bruce Wetzal and Harry Schaefer, National Cancer Institute, National Institutes of Health

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Bone modifying agents such as bisphosphonates were initially used to reduce osteoporosis and fractures in AI-treated patients and patients with bone metastases. They have now also been shown to reduce recurrence rates of breast cancer in the adjuvant setting, but only in post-menopausal women.¹³

On the horizon are new and more effective SERDs. These can be administered orally, and have been shown to have greater preclinical activity compared with fulvestrant, including in *ESR1* mutant models.¹⁴

Finally, there is increasing evidence of interplay between sex steroid receptors, including the ER and androgen and progesterone receptors (AR and PR),¹⁵ Therapeutic strategies that modulate ARs and PRs are being evaluated in ER-positive breast cancer.

In summary, there is a renaissance in the treatment of ER-positive breast cancer. The therapeutic repertoire in the management of our patients has never been as diverse as it is today.

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www.endocrinology.org/endocrinologist/122-winter16.

ENDOCRINOLOGY AND BEHAVIOUR: A STRESS-FREE APPROACH TO IMPROVING ANIMAL WELFARE

WRITTEN BY TESSA E SMITH



'HAPPY' ANIMALS MAKE BETTER SCIENTIFIC SUBJECTS

Since the Animal (Scientific Procedures) Act 1986 was implemented in the UK, there has been a plethora of research combining endocrine titres with behavioural measures to address applied questions in the field of animal welfare science. The goal of these studies has been to measure and optimise animal welfare.

One eloquent example is the reduced welfare observed in collared peccaries (*Pecari tajacu*), as indicated by high glucocorticoid (GC) levels and negative judgment bias in behavioural tests. The latter is associated with space restriction, but alleviated by the provision of enrichment.¹

Good animal welfare is essential not only from an ethical standpoint but also to ensure valid scientific outcomes. Animals with good welfare produce more reliable, biologically valid, robust, repeatable scientific data when compared with their counterparts with poorer welfare. 'Happy' animals live longer, can be used repeatedly and need replacing less often. This leads to a 'reduction' in animal use and satisfaction of one of the 3Rs (the guiding principles for the use of animals in research).²

THE 'STRESS' RESPONSE

Exposure to a physical or psychological 'stressor' causes a cascade of physiological reactions that enable an animal to cope via a dynamic process of change termed allostasis. There is no uniformly accepted definition of 'stress', but here I define 'stress' as a 'real or perceived threat to homeostasis' with the caveats of uncontrollability and/or unpredictability.^{3,4}

A primary physiological response to a 'stressor' is activation of the hypothalamic-pituitary-adrenal (HPA) axis and concomitant release of GCs. In the short term, GCs trigger adaptive responses that enable the body to cope with the 'stressor', such as mobilising energy stores.

Chronic stress and GC exposure are, however, extremely damaging. The latter causes, for example, suppressed reproductive and immune function, diminished cognitive ability, impaired tissue repair and compromised neuronal development in the brain, particularly in the pre-frontal cortex.

GCs have an impact on other regulatory systems, however, in addition to those dealing with 'stress' – such as the mesolimbic dopaminergic reward system. Rewarding experiences such as feeding, social defeat and consensual sex also trigger GC release.⁴ It is thus essential that, if titres of GCs are to be used to evaluate 'stress' and inform welfare decisions in animals, additional measures should be used to correctly interpret GC levels. One quantitative tool, empirically validated as a reliable measurement of 'stress', is behaviour measurement.

PAIRING ENDOCRINOLOGY WITH BEHAVIOUR

At the simple end of the spectrum, high levels of GCs co-existing with certain behavioural traits or frequencies that deviate from those observed in the wild population, such as stereotypic pacing in polar bears (*Ursus maritimus*), are taken to imply that an animal is 'stressed' and potentially experiencing poor welfare.⁵

These types of data can inform management decisions. Environmental correlates of high GCs and stereotypic pacing in polar bears, such as exhibit size, can be modified to improve welfare. This effective pairing of endocrine and behavioural parameters has led to the development of behavioural stress scores (BSSs). These are defined as a set of behaviours, each with an identified sliding scale assumed to indicate varying degrees of 'stress'.

In their best form, BSSs are underpinned and validated by established physiological indicators of 'stress', such as GC titres. For example, our

'Animals with good welfare produce more reliable, biologically valid, robust, repeatable scientific data when compared with their counterparts with poorer welfare.'

laboratory is currently developing a BSS to permit objective non-invasive assessment of welfare in captive amphibians, thousands of which are housed in captivity for research, education, captive-breeding and as pets. However, comprehensive, consensually developed best practice guidelines for housing and husbandry that provide optimal welfare are lacking. We are developing a putative scale of behaviours (such as ‘walling’ – rapid swimming backwards and forwards along a tank wall) that we have shown to be associated with varying degrees of corticosterone release (which we quantify from the tank water around the subject).

In the domestic horse (*Equus ferus caballus*), we have taken this one step further by identifying behaviours for a BSS such as repetitive crib-biting that are correlated with not one but two established physiological indicators of ‘stress’, i.e. titres of salivary cortisol and heart rate.⁶ In this way, the pairing of endocrine with behaviour parameters can produce reliable, empirically validated, easy to implement measures of animal welfare.

‘The pairing of endocrine with behaviour parameters can produce reliable, empirically validated, easy to implement measures of animal welfare.’

A CIRCULAR WELFARE SCENARIO

Welfare studies that pair endocrinology with behaviour usually extract GC metabolites from sample media that can be collected non-invasively, such as urine, faeces or saliva. This approach is taken because procedures associated with taking a blood sample, such as restraint and venepuncture, typically raise HPA function and artificially raise GC levels or mask results of experimental treatments.

Golden lion tamarin. ©Shutterstock



Polar bear. ©Shutterstock

Behaviour theory is implemented to collect these non-invasive samples. Animals are trained using operant conditioning theory (i.e. positive reinforcement techniques; PRTs) to ‘voluntarily donate’ their sample. For instance, trained animals will urinate into a cup upon presentation of a cue: a behaviour shown to take as little as five 30-min sessions to train in the golden lion tamarin (*Leontopithecus rosalia*).⁷

Ironically, this use of behaviour as a tool to collect endocrine samples (for welfare studies) affects well-being itself (possibly via the perception of increased controllability). For example, captive common marmosets (*Callithrix jacchus*) involved in PRT programmes were better able to deal with routine husbandry stressors such as weighing than their laboratory partners not involved in such a programme.⁸ Similarly, wolves (*Canis lupus lupus*) participating in PRT had reduced levels of salivary cortisol post-training compared with pre-training.⁹

Thus, experimental evidence shows that participation in PRT programmes improves the welfare of the subjects – the very construct it set out to test.

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WORKING AT THE INTERSECTION: CROSS-DISCIPLINARY ENDOCRINOLOGY

Josef Köhrle and Gail Risbridger are, respectively, Editor-in-Chief and Senior Editor of the Society's open access journal *Endocrine Connections*. Here, they discuss the opportunities and challenges associated with working at the intersection of endocrinology and other related disciplines in medical science.

A multidisciplinary approach to research is not a new concept. Increasingly, it is being recognised favourably by the funding bodies that make decisions about grant applications. Many see it as having a greater potential to solve 'real-world problems' than specific research within a single discipline. When a cross-disciplinary team works well, the reciprocal interactive relationships ensure that all participants focus on the ultimate goal. Rather than conducting experiments or testing hypotheses simply because they can be done, the focus is set firmly on what needs to be achieved to provide proof of concept.

As the scientific discipline of biological communication via hormones, various mediators, their receptors and a multitude of intracellular signalling

pathways, the field of endocrinology has inherent cross-disciplinary potential. Together with neuronal, immunological, nutritive and – of recent interest – environmental factors, the highly versatile endocrine system is key to maintaining a homeostatic balance between living organisms and the challenges presented by their environment.

Health and disease, reproduction, survival and ageing are controlled by hormones. They perform the essential biological communication within multicellular organisms, affecting their various organs, and controlling their responses to nutrients and the environment.



GAIL RISBRIDGER

For many researchers, the widespread application of endocrinology across the medical sciences presents opportunities to be involved in interdisciplinary research. As Research Director of the Monash Comprehensive Cancer Consortium (Melbourne, Australia), and after training in reproductive endocrinology, I work at the intersection of cancer research and endocrinology. For my own field of prostate cancer, an endocrine training and background are essential, as the main focus of therapies is to block androgen signalling.

My endocrine background is also a terrific advantage. As more men receive androgen deprivation therapy, the consequences, such as obesity, diabetes and osteoporosis, make the role of the endocrinologist even more important in patient management. To maximise the potential benefits of cross-disciplinary co-ordination, urologists, oncologists and pathologists collaborate closely and even research scientists attend the multi-disciplinary team meetings.

Endocrinology's broad relevance across the medical sciences means much research is potentially interesting to a wide range of other researchers, clinicians and medical practitioners who may not class themselves as endocrinologists. Nevertheless finding a suitable place to publish and disseminate this work can be challenging because of the diverse target audience.

Researchers working in fields that closely intersect with endocrinology, such as cancer, ageing, dermatology and cardiology, may not fully appreciate the relevance of their research to other disciplines. Publishing in specialist journals makes it less likely that the findings may be read by endocrinologists.

GAIL RISBRIDGER is Research Director of the Monash Comprehensive Cancer Consortium and at Monash University, Melbourne, Victoria, Australia. Her research includes stromal-epithelial cell interactions in normal and cancerous prostate using tissue recombination, animal and human specimens.



JOSEF KÖHRLE

Even within the field of endocrinology, the scopes of traditional peer-reviewed journals tend to be fairly specific, covering core endocrine topics such as research on endocrine glands, or the stereotypical endocrine disorders of obesity and diabetes.

Endocrine Connections, the Society for Endocrinology's interdisciplinary journal, satisfies the growing need for a cross-discipline publishing outlet for endocrinology. The journal links the medical disciplines dealing with processes influenced by, and modulating, the hormonal system.

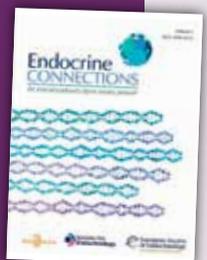
There is a special focus on those organs which are not typically considered as endocrine glands or tissues, but which are strongly involved in endocrine regulation and homeostasis. 'New' endocrine-active tissues, such as liver, adipose tissue, muscle, the gastrointestinal tract with its microbiota, the heart and cardiovascular system, as well as the central nervous system, are all covered by *Endocrine Connections*.

Given the increasing number of opportunities available to endocrinologists to collaborate with medical practitioners and researchers from other disciplines, it seems that overcoming the challenges associated with interdisciplinary research is becoming more and more worthwhile, and has the potential to allow endocrinologists to contribute to closing some of the large knowledge gaps that remain in the medical sciences.

JOSEF KÖHRLE is Chairman of the Institute for Experimental Endocrinology at the Charité-University Medicine, Berlin, Germany. His interest centres on thyroid hormones and their metabolites, particularly regarding energy metabolism and regulation of body weight.

Endocrine Connections is the Society for Endocrinology's official open access journal. Now in its fifth year of publication, the journal is indexed in PubMed Central and the Science Citation Index Expanded. It addresses the core of endocrine communication: the hormonal connections between individual body parts and the whole healthy or diseased living organism (typically human).

Members of the Society for Endocrinology benefit from a discounted publication charge of just £765. You can find out more at www.endocrineconnections.com.





ALL YOU NEED IS ENDOCRINOLOGY?

FROM OUR SCIENCE COMMITTEE CORRESPONDENT

It was once possible for a scientist to know pretty much everything. In the 18th and 19th centuries, science was largely a niche concern for amateur gentlemen of independent means, who were attracted to such a career by the unprecedented opportunities to brood moodily over exotic-looking glassware, reanimate frogs, and establish the laws at the heart of existence.

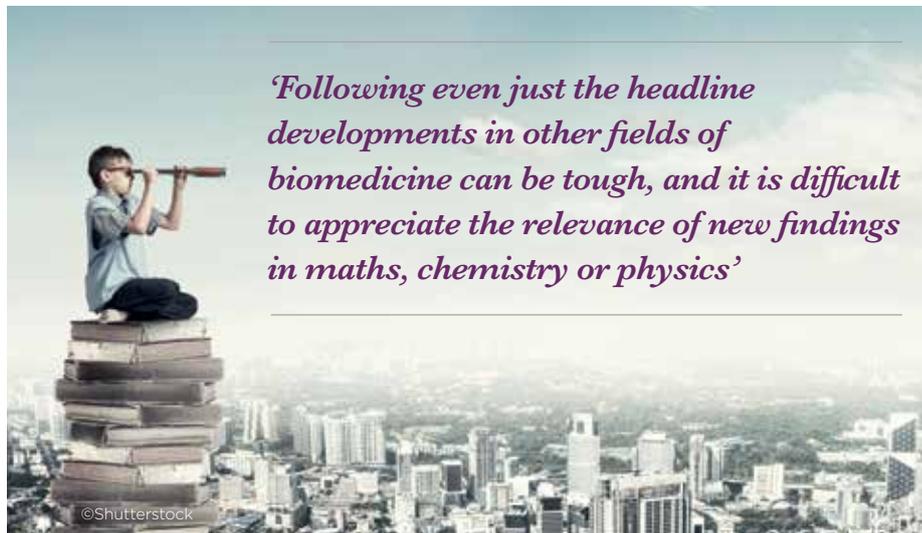
Though you might have needed patience to source particular texts (the search engines of the day were more prone to bugs), you could feasibly read almost everything that was published across all disciplines. Darwin notoriously read widely, including virtually all of the works of natural history of renown that were published before and during his lifetime (with the notable exception of a particular Austrian monk's work on peas, though the pertinent editions of *Verhandlungen des naturforschenden Vereins Brünn* were no doubt next on his 'must read' list).

Since then, science has dramatically expanded and, with this expansion, it has fragmented into hundreds of subspecialties. Such specialisation raises problems. Multidisciplinary projects are encouraged, but can founder on misunderstandings and miscommunication; in some fields, even understanding the important questions requires significant specialist training. The rate at which new findings airily wash into our inboxes can be overwhelming.

Science has also professionalised, and most academic positions come with significant responsibilities beyond conducting research.

During busy periods, it can be difficult keeping up with the work in our own particular areas of interest, let alone endocrinology as a whole. Following even just the headline developments in other fields of biomedicine can be tough, and it is difficult to appreciate the relevance of new findings in maths, chemistry or physics.

The theme of this issue of *The Endocrinologist* is 'endocrinology at the centre of everything', and certainly endocrinology is a large and intersection-grabbing circle in the Venn diagram of biomedical science, well placed to facilitate interactions between different areas of physiology. Hormones affect every organ in the body, and are released from nearly as many. But influence works in both directions, and ideas from other disciplines can offer insights into one's own.



'Following even just the headline developments in other fields of biomedicine can be tough, and it is difficult to appreciate the relevance of new findings in maths, chemistry or physics'

It becomes easy to think of reading as an 'extra' we carry out in the interstices within our real work. When time is short, we may concentrate on keeping up with incremental findings in our specialities, rather than big discoveries in other fields. It's taken for granted that Darwin's breadth of reading allowed his thinking to be shaped by influences such as the geologists Lyell and Hutton and the economist Malthus. But we perhaps underestimate what a commitment this took. Darwin's notebooks and reading lists show how reading was a major component of his scientific work, as important to his findings as his experiments and voyages of discovery, and one which required significant effort.

Alas, I suspect that I have other intrinsic limitations which prevent me from coming up with ideas as good as, say, evolution by natural selection. Nevertheless, to better realise the importance of endocrinology, we perhaps need to put aside the time to learn about other subjects. For example, the 2 hours a week I spend complaining about how busy I am could be usefully repurposed.

'And what should they know of endocrinology, who only endocrinology know?' as I believe Bayliss, or perhaps Starling, once said...

KEVIN MURPHY
Science Committee correspondent

To get in touch with the Society's Committees, email members@endocrinology.org

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DEPARTMENT OF MAINTENANCE

WRITTEN BY TONY COLL

Deny it if you want chaps but, as we age, the need to carp on about the minutiae of design and function (especially regarding bikes, see *The Endocrinologist*, passim) becomes ever more urgent. Partners and offspring may mistakenly dismiss this phenomenon as ‘becoming boring’ or ‘turning into your dad’. I prefer to think of it as a something of a second childhood, with great pleasure to be had in rediscovering the beauty of high functionality and cracking solutions to age-old problems.

One such problem that has faced humankind since the first days of cave dwelling is how to keep the rain out but let the light in. You may have given this little thought of late, but take a minute to look around your house or office to see the various attempts to address this.

Having just finished rehangng one in an upstairs room, I am currently of a mind that one of the most satisfying solutions to the window problem is the double hung, boxed, vertical sash. When I had finished the job, I had to



assemble the family to watch me open it. Then shut it. Then open it again and let some rain in. Child 2 (with headphones) looked at me in silence before shuffling off, muttering something about why we cannot get builders in like normal people.

Ask me about windows at your peril. Be prepared to engage in earnest conversation around mullions and parting beading, on the thermal physics that mean opening both top and bottom sash allows hot air to escape and cool air to be drawn in, about the beauty that is the Venetian tripartite.

So what, and who cares? Well anything that can combine seamlessly blending in with being so fit for purpose is worthy of further thought. Sash windows do what they do so well that they are often taken for granted. But their silent work ethic belies the craftsmanship and skill beneath and, as such, they are rich in allegorical content.

The window now restored was made from slow grown, seasoned wood that was meant to last for over a century (and has done so). Beneath the flat white exterior is a hidden mechanism that works every time, the result

of craftsmanship nurtured over generations. In return for years of loyal, unquestioning service, the deal is that every 10 years someone has to undertake a little maintenance to enable more years of untroubled service: sash cords grow worn, paint flakes from wind and sun, timbers twist and tighten. Yet, this key activity looked to be time-consuming and unappealing, and previous owners had neglected their duties.

So here is the clunking analogy, as I look around the wider clinical arena. Across the patch, I am fortunate to work with highly skilled individuals who have been doing what they do so well and for so long that a naïve observer could mistake their job to be a simple one. They’ve done a few decades and are now facing a few more. Having weathered storm after storm, a less lustrous patina and the odd squeak are inevitable. With no fatal flaw and still wholly fit for purpose, being designed properly in the first place, they are in desperate need of maintenance before more irreversible damage is done. Yet these folk are not resting easy and wonder what lies ahead, particularly as the outside environment has become more hostile.

People arrive to assess, but do they have an appreciation of what they are trying to maintain? Surface damage must surely mean deeper rot: better to rip the lot out and bang in replacements in a day. Give it a 10-year guarantee and then it’s someone else’s problem.

But hang on, that’s still too costly, so maybe just paint over the cracks and hope that there are not going to be too many heavy frosts this winter. The

‘If we have any chance of coming through the months and years ahead unscathed and still fit for purpose, we need to be more mindful of the need for maintenance and somehow factor this in to our activities and timetables.’

immediate cosmetic result is initially appealing, but provides only a short term solution for a longer term problem and runs the risk of causing major structural damage to a fragile organic system.

OK, enough already. Of course clinicians are more than cords, pulleys and timber. But I remain concerned that it is all too easy for health professionals to yomp on, in the belief that they are made of the right stuff and that is sufficient to see them through. It might for some, but others can easily falter and that would be a waste and a shame.

If we have any chance of coming through the months and years ahead unscathed and still fit for purpose, we need to be more mindful of the need for maintenance and somehow factor this into our activities and timetables. A little genuine attention, some sanding down of roughened edges and a new coat for the winter can work wonders.

TONY COLL
Editor, *The Endocrinologist*

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Adrenal and Cardiovascular Network AN UPDATE



We have recently made great strides in enhancing our understanding of the pathophysiology underpinning adrenal and cardiovascular disease.

There have been significant advances in our knowledge of the genetic basis of adrenal tumours, and the use of novel imaging modalities is gaining momentum alongside the exploratory use of biomarkers as an adjunctive clinical tool. In addition, it is now recognised that there is an underlying endocrine basis in up to 10% of subjects with hypertension, including primary aldosteronism, phaeochromocytoma/functional paraganglioma and Cushing's syndrome.

'We are delighted that more than 200 people have registered an interest in being part of this Network'

Yet we are still faced with significant challenges to address. The increasing use of cross-sectional imaging as an investigative tool in clinical medicine and the resultant identification of incidental adrenal tumours is a growing clinical issue. Adrenal insufficiency, due to a variety of disorders (including prescribed steroids), is also associated with increased mortality and morbidity, and there is still a need to ensure that it is managed appropriately. This is particularly the case in the acute setting, where adrenal crisis is a genuine medical emergency that is associated with a significant mortality.

The Adrenal and Cardiovascular Network aims to bring together clinicians and basic scientists, and junior and senior colleagues, to address many of

these issues. We are delighted that, to date, more than 200 people have registered an interest in being part of this Network.

As well as suggesting relevant symposia for consideration by the Society for Endocrinology BES Programme Committee, and proposing nominees for prizes and awards to the Nominations Committee, we are keen to act as a forum for teaching and training in adrenal pathology and endocrine hypertension.

We want to promote public engagement through links with established patient support groups including the Addison's Disease Self-Help Group (www.addisons.org.uk) and by providing a panel of experts to address media and public enquiries. In addition, we aim to facilitate interactions between clinicians and researchers to develop high quality research proposals with the potential to change clinical practice.

If you are interested in being part of the Network please contact us and share your thoughts – we need your input to make this Network a true success.

JEREMY TOMLINSON & ELEANOR DAVIES
Endocrine Network Convenors

Find out more at www.endocrinology.org/endocrinenetworks or contact debbie.willis@endocrinology.org.

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20–21 March 2017

Hilton Birmingham Metropole Hotel, NEC, Birmingham, UK

Apply for a travel grant before 15 December. Register at:
www.endocrinology.org/events/endocrine-nurse-update



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Clinical UPDATE

20–22 March 2017

Hilton, Birmingham Metropole Hotel,
NEC, Birmingham, UK

Submit your case by 9 January.
Register at:
[www.endocrinology.org/events/
clinical-update](http://www.endocrinology.org/events/clinical-update)



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An interview with...

GRAHAM WILLIAMS

THE NEW SOCIETY PRESIDENT

The Society's new President, Professor Graham Williams, began his term of office at the recent Society for Endocrinology BES conference. He has been a leading contributor to the Society's success, most recently as Treasurer (2010–2015). Here, Graham talks to Amir Sam about his life inside and outside endocrinology, and what he is looking forward to during his time as President.

WHO WERE YOUR EARLIEST MENTORS?

My primary school headmaster always said, 'Whatever talent you have, you must make the most of it.' That was the first thing that really struck me.

At secondary school, I was influenced by two important people. The first was my French teacher, who also coached football. I was captain of the school team and he instilled in me a lot of things about discipline, perseverance and leadership. The second was my chemistry master, who got me interested in chemistry and laid the foundations for my fascination with science.

However, I think my parents were the biggest influence of all. They had a very liberal attitude, and strongly encouraged me to follow whichever path I wanted. They were endlessly supportive.

TELL US MORE ABOUT YOUR PARENTS...

My father was orphaned at a young age and left school when he was 14 to work in his uncle's bakery in Poulton-le-Fylde, Lancashire. He later got a job as an articled clerk in an accountant's office, and worked his way up to become a senior partner in a large international accountancy firm.

My mother's mother was the daughter of a gardener on the Chatsworth Estate in Derbyshire. She worked in a cotton mill and married a steeplejack from Huddersfield. They moved to Blackpool, where my mum was born. My mother worked as a secretary in a local firm of solicitors.

My mum and dad never had the chance of further education, so I was extremely fortunate that they gave me every possible opportunity and encouragement as I grew up.

WHAT LED YOU TO A CAREER IN MEDICINE?

Medicine was never a calling that I had particularly considered. Like all boys growing up in Manchester, I wanted to be a professional footballer but, unlike most footballers, I was good at languages! I also liked to construct and develop arguments, so I was initially attracted to law and wanted to be a barrister.

However, my father specialised in assessment of damages and compensation. He spent a lot of time in London giving evidence in fraud and personal injury cases. Ultimately, I felt I wanted to pursue something completely different and so, around the time of my A-levels, I moved into the sciences.

'I think my parents were the biggest influence of all. They had a very liberal attitude, and strongly encouraged me to follow whichever path I wanted. They were endlessly supportive.'



This was perhaps because it was more of a challenge, and also because the job prospects at that time were better.

In the end, I felt that medicine would allow me to keep my options open as much as possible in science. Really though, I was driven by discovery and originality.

WHO INFLUENCED YOU MOST AT MEDICAL SCHOOL?

I went to St Thomas' Hospital Medical School in London and had a fantastic time in a small year of 60 students with a great family atmosphere of camaraderie. I did a BSc in anatomy, and the professor of the department, Michael Day, along with Marion Kendall in the histopathology department, were the first to get me really interested in research. I worked with them on the ultrastructure of the ureter in the wild starling and published my first paper while a medical student.

SO WHAT DREW YOU TO ENDOCRINOLOGY?

When I qualified from medical school I was all set to do surgery, but realised pretty quickly that I did not have the dexterity to be any good. My first house job was in endocrinology at the Queen Elizabeth Hospital in Birmingham with David London. At the time, there were some really fascinating cases, and working with him got me enthused and hooked on endocrinology straight away. He definitely had the biggest influence on my choice of career.

TELL US ABOUT YOUR TRAINING AND EARLY CAREER...

I worked as a Senior House Officer in Kidderminster, Worcestershire, and did my general medicine rotation at the Queen Elizabeth and Birmingham General Teaching Hospitals. I then got an MRC Training Fellowship with Michael Sheppard and Jayne Franklyn in Birmingham to work on thyroid hormones. I did a year of my PhD there and completed it at Harvard Medical School with Reed Larsen and Greg Brent at the Brigham and Women's Hospital in Boston, MA, USA, where I also did some of my post-doctoral training.

I came back with an MRC Clinician Scientist Fellowship to be a lecturer in Birmingham, where I had a completely empty lab and had to start from nothing! About 6 months before I left Boston, I had a meeting with Reed, who was very happy to support me, but said that I shouldn't work on the same subject as him, because it was too small a field and I needed to develop my independence. He urged me to read the literature and find a new area to pursue.

I had been working on the biochemistry of transcriptional activation by thyroid hormone and retinoid X receptors, and wanted to apply the basic science to clinically and physiologically important questions. I decided to find a relevant thyroid hormone responsive target tissue that wasn't being studied. Most people were working on pituitary, heart and liver, and other labs were getting into the brain.

'I felt that medicine would allow me to keep my options open as much as possible in science. Really though, I was driven by discovery and originality.'



I spent a lot of time talking to a range of people, and eventually settled on the skeleton, a clearly important target organ that had not been investigated in the context of thyroid hormones in any detail. Having not known anything about bone, I had a blank canvas and started from scratch! In 1995, I was approached by Raj Thakker and James Scott to move to the Hammersmith Hospital in London as a senior lecturer.

IS THERE A PAPER THAT YOU ARE PARTICULARLY PROUD OF?

When I moved to the Hammersmith Hospital, I had to set up the lab and the administrative burdens were getting bigger. However, I was determined to work at the bench and publish something on my own before having to focus more on lab supervision. Eventually, in 2000, I published a single author paper in *Molecular & Cellular Biology* (20 8329–8342) entitled 'Cloning and characterization of two novel thyroid hormone receptor β isoforms'.

AS TREASURER AND NOW PRESIDENT, YOU WILL OVERSEE MORE THAN A DECADE OF DEVELOPMENT AT THE SOCIETY. WHAT HAS BEEN AND WILL BE THE BIGGEST CHANGES?

The financial aspect of the Society has substantially increased over time. When I became Treasurer, the gift aid to the Society from Bioscientifica was around £100,000 per year, while by the end of my term it had grown to about £1 million per annum. The Society has grown incredibly in terms of its diversity; it is reaching out further to different countries and continents in a way that was never possible previously. It is now a very professional and superbly run organisation.

I don't think my plans for the future will be to fix anything in particular, because I believe the Society is functioning extremely well. We have a greatly increased role in education and the development of opportunities for young endocrinologists. We need to develop the Society further along these lines for the benefit of the next generation. We must support our younger scientists and clinicians, retain them and hopefully attract more people to the discipline, with the ultimate aim of benefiting our patients and endocrine science. We also need to strengthen our international collaborations, both scientifically and clinically.

'The Society has grown incredibly in terms of its diversity; it is reaching out further to different countries and continents in a way that was never possible previously.'

WHAT ABOUT YOUR INTERESTS OUTSIDE ENDOCRINOLOGY?

I like to be active and am a keen sportsman. I have spent a lot of time walking and scrambling in the Lake District. I used to go there with my brother and for family holidays, and still enjoy fell-walking there and in Scotland whenever I get the chance.

I have been a very keen footballer all my life and played to a good standard until my mid-40s, when the inevitable knee injury and cartilage surgery ended my deteriorating career! My family have been Manchester United supporters for ever and my dad bought season tickets at Old Trafford just after the World Cup in 1967. My greatest hero was George Best and the memories of watching him play every week are still very vivid today – there is simply no one to touch him and I doubt there ever will be.

CONTINUED ON PAGE 22...

...CONTINUED FROM PAGE 21

On holiday, when my son was about 8 years old, we played crazy golf and he became obsessed with the game! He subsequently had golf lessons and we found out he was pretty talented, and they encouraged him to join a proper club. So we both joined at Ealing together: he ended up playing county golf for Middlesex and now plays at university and for a club in Cornwall, while I play competitively as well.

I also cycle to work every day and have done so for over 15 years, although it is strictly commuting and I am not a recreational cyclist. Much to my wife's chagrin, I am an appalling swimmer, and so water sports are a real no-no for me!

CAN YOU RECOMMEND A GOOD BOOK?

I have always read a lot, especially novels that deal with social commentary and tell a good story; John Steinbeck, Ernest Hemingway and Émile Zola have been particular favourites. My current interest is in police procedural novels. There is a superb series of ten books by Maj Sjöwall and Per Wahlöö about a Swedish detective called Martin Beck. They are set in the 1970s in the context of policing in Stockholm at the time of political unrest and the Cold War. I've been captivated by their realism and the economical way in which they are written. They're absolutely superb and highly recommended!

DOES YOUR FAMILY SHARE YOUR INTERESTS?

My wife, Shirley, comes from Birmingham. She was the sister on the coronary care unit at the Queen Elizabeth Hospital, so we met at work in the classical way. Her parents are both Scottish: her mum is from Fife and her dad from Edinburgh. She loves tennis and plays for a local club and she enjoys swimming – but she really does not like football! My son, Edward, is at Falmouth University studying product design and enjoying the outdoor life in the South West. As I mentioned, we share a love of golf. My older

brother was a very keen rock climber and has worked in various outdoor pursuits shops. He is now a manager in a store in Manchester. My younger sister is a practice nurse in Oxfordshire.

'Always try to find a way to say yes to help other people; that attitude will always stand you in good stead.'

FINALLY, WHAT ADVICE WOULD YOU GIVE A YOUNG ENDOCRINOLOGIST?

First, don't be daunted by any question. Most things can be achieved, so if you really want to do something don't be put off, just go for it – you need to be 'on a mission'! Make use of your ingenuity and persistence, and work hard.

Secondly, don't waste time doing bad research! Reed Larsen always used to say, 'I can never understand why people do bad research because there is never enough time to do good research.' The real message here is to think hard about what you do and who to do it with. Planning and preparation are really very important and essential for success.

Lastly, always try to find a way to say yes to help other people; that attitude will always stand you in good stead.

Graham Williams was interviewed by Amir Sam, Associate Editor of The Endocrinologist.

Graham (here pictured with Julia Buckingham, former President of the Society) was awarded the Society for Endocrinology medal in 2011. This medal is awarded to an endocrinologist working in the UK in recognition of outstanding studies.



A life-saving initiative: ENDOCRINE EMERGENCY GUIDANCE

WRITTEN BY MARIE FREEL



Endocrine emergencies are potentially life-threatening clinical problems, and are compounded by a lack of recognition, leading to delays in therapy. Every endocrinologist is aware of patients, attending their outpatient clinic, with tales of suboptimal care in a non-endocrine clinical environment, because of a failure to understand their chronic condition and its possible complications. This is particularly relevant in adrenal insufficiency, and has led to potentially avoidable excess morbidity and mortality.

To address this issue, the Society's Clinical Committee has launched a new initiative to introduce succinct and straightforward clinical guidance documents for use by the non-endocrinologist within an emergency setting. Five 'Emergency Guidance' documents have been developed, often in conjunction with more comprehensive European, American or national guidelines.

All five have been published together in *Endocrine Connections*.¹⁻⁵ Each covers the most common endocrine-themed medical emergencies.

ADRENAL INSUFFICIENCY¹

This is often under-recognised and, in particular, there is a lack of understanding of 'sick day rules' amongst non-endocrine health professionals. This Emergency Guidance document clearly outlines key points in the recognition and management of a new presentation of adrenal insufficiency, as well as clarifying how to alter glucocorticoid therapy in the event of intercurrent illness or medical procedures. The lead author, Wiebke Arlt, was also an author of the Endocrine Society clinical practice guideline on the diagnosis and treatment of primary adrenal insufficiency published in 2016.⁶

'The Society wishes to distribute these documents widely to a non-endocrine audience, most notably emergency departments and acute general medical and surgical wards.'

SEVERE SYMPTOMATIC HYPONATRAEMIA²

This Emergency Guidance document has principally been written by Stephen Ball, who was also an author of the European Society of Endocrinology clinical practice guideline on hyponatraemia in 2014.⁷ The particular strength of this guidance is that it emphasises the importance of assessing the severity of acute hyponatraemia and treating it accordingly in the first instance. Evaluation of volume status and confirming the exact cause of hyponatraemia, whilst important, are often done poorly by non-specialist clinicians, and delay the appropriate treatment of this common and potentially life-threatening condition.

ACUTE HYPOCALCAEMIA AND HYPERCALCAEMIA^{3,4}

Disorders of calcium regulation are the second-most common electrolyte disorder requiring endocrine input. In these Emergency Guidance documents, Jeremy Turner, Jennifer Walsh and colleagues provide a concise summary of the key causes of hypocalcaemia and hypercalcaemia and their immediate management, based upon biochemical severity and underlying cause. In the case of hypercalcaemia, the first step is rehydration with normal saline, and intravenous zoledronic acid is now the bisphosphonate of choice.

QUICK LINKS TO THE EMERGENCY GUIDANCE DOCUMENTS

Distribute these to your colleagues in emergency departments and general medicine.

Adrenal insufficiency	http://dx.doi.org/10.1530/EC-16-0054
Hyponatraemia	http://dx.doi.org/10.1530/EC-16-0058
Hypocalcaemia	http://dx.doi.org/10.1530/EC-16-0056
Hypercalcaemia	http://dx.doi.org/10.1530/EC-16-0055
Pituitary apoplexy	http://dx.doi.org/10.1530/EC-16-0057

PITUITARY APOPLEXY⁵

In this condition, recognition and prompt treatment with intravenous hydrocortisone may be life-saving and prevent long term visual complications. In this Emergency Guidance document, Stephanie Baldeveg and colleagues emphasise that this condition must be considered in patients with acute severe headache, visual defects and/or impairment of consciousness. Authors of this document were also authors of the Society for Endocrinology's UK guidelines for the management of pituitary apoplexy, published in 2011 and reviewed with no necessary changes in 2014.⁸

Each Emergency Guidance document has been principally written by authors with extensive experience and expertise in the relevant condition with consideration of the most up to date evidence available, and has been peer-reviewed by the Society for Endocrinology Clinical Committee.

The Society wishes to distribute these important documents as widely as possible to a non-endocrine audience, most notably emergency departments and acute general medical and surgical wards. Publication of all documents in *Endocrine Connections* and subsequent availability on the Society for Endocrinology website will allow endocrinologists to provide a single point of reference to non-specialist colleagues to guide the management of these extremely common and important conditions.

MARIE FREEL

On behalf of the Society for Endocrinology Clinical Committee

This article has been reproduced in amended form from Endocrine Connections 2016 5 E1-E2. doi:10.1530/EC-16-0068

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TALKING FACE TO FACE: THE VALUE OF THE SOCIETY'S THEMED SCIENTIFIC MEETING GRANT

WRITTEN BY JASON CARROLL



Jason Carroll recently received the Society's Themed Scientific Meeting Grant to run a conference on hormone-dependent cancers. Here, he tells us why he applied for the award and how it has benefited his area of science.

Hormone-dependent cancer is commonly seen as an 'old' and 'mature' area of work, particularly when viewed next to some cancer types that are only now being characterised. However, two major variables keep hormone-dependent cancers in the spotlight.

The first is that oestrogen receptor (ER)-positive breast cancer and androgen receptor (AR)-driven prostate cancer continue to kill thousands of people every year. This is despite the existence of endocrine therapies that block ER and AR activity in breast and prostate cancer respectively.

Secondly, recent technological advances in '-omics' and cancer modelling have revealed extraordinary insights into hormone-dependent cancers that we simply didn't appreciate a few years ago. We now know that endocrine resistance can arise due to changes in the fidelity of ER and AR themselves, and that existing agents that block these proteins lack efficacy in these situations.

This has clarified the need for better targeted agents that can modulate these pathways indirectly, which requires an understanding of the biological basis of ER/AR activity. In addition, recent advances in cancer modelling have meant that we can study hormone-dependent cancer in a more physiologically relevant and robust manner.

'Being able to discuss ideas "offline", and to brainstorm, are crucial parts of knowledge transfer. This can lead to successful collaborative efforts.'

FACILITATING COLLABORATION

Our field is changing so fast that it's sometimes challenging to keep up with new discoveries and publications. Wayne Tilley (my collaborator from the University of Adelaide, SA, Australia) and I thought it was critical for us to gather some of the leaders in the field together, in order to present new findings and to discuss and share ideas.

Being able to discuss ideas 'offline', and to brainstorm, are crucial parts of knowledge transfer. This can lead to successful collaborative efforts. As such, having key people together in one location with the time for discussion and debate is vital.

ACHIEVING A BROAD REACH

The meeting we organised in Cambridge (UK) included some of the people who are most central to changing paradigms and shaping our understanding of these important cancers. We were keen to ensure that the

meeting reflected the different aspects of the research area, including novel biological understanding, evolving cancer models and new preclinical and clinical observations.

A number of exciting new treatment options are available for women with ER-positive breast cancer and men with prostate cancer but, in many cases, we don't know how to stratify patients appropriately, because we're still not sure who will benefit from specific treatments and who will not. This meeting was designed so that new clinical findings could be discussed in the presence of the biologists and clinicians who are learning about the cancer specific variables, to facilitate better patient stratification. This integrative approach is required in order to maximise the success of new therapies.



Delegates at the Cambridge Meeting. Jason Carroll

THE IMPORTANCE OF FUNDING

Both of us who organised this meeting have an excellent long-standing relationship with the Society for Endocrinology. When we heard about the funding opportunity provided by the Themed Scientific Meeting Grant, we were keen to apply. Once we had gone through the application process, what was most striking was how easy and user friendly it had been. It was not at all complicated or laborious and we received a response quickly – this is in stark contrast to many other funding agencies.

Organising a conference such as we did, with world-leading speakers, requires funds to ensure we could cover the running costs and the speakers' travel and accommodation. Without this support, speakers of a high calibre wouldn't have attended. This is why it's important such conference funding opportunities are available, and why we are so grateful for the funds we received from the Society of Endocrinology.

We were delighted with the conference, and hope that we can run similar meetings again in the near future.

JASON CARROLL

Group Leader, Cancer Research UK Cambridge Institute

The Society's Themed Scientific Meeting Grant provides up to **£10,000** to support the best new science by funding short, focused scientific meetings. The next application deadline is 31 May 2017. You can find more information at <http://bit.ly/2eH411z>.

'PUBLISH OR PERISH': NO LONGER THE MANTRA OF ACADEMICS?

WRITTEN BY VICTORIA MERRIMAN

Astonishingly, 2 million new papers are now published annually. However, the time available to find and read articles has not increased correspondingly. The result is that around 50% of published research papers are never read, and 90% never cited.

Academics are consequently at increased risk of 'publishing *and* perishing', giving rise to a new mantra: 'be visible or vanish'. It's becoming crucial to raise your research above the parapet by promoting it. This new step is recognised in modern academia, as grant applications increasingly require researchers to demonstrate the *impact* of their research, rather than just the quantity.

The idea of self-promotion may seem daunting (and perhaps not natural), but this three-step guide should set you on your way.

1. YOUR UNIQUE SELLING POINT

Establish what about your paper is new and important, and then create content to promote this. It could take the form of an infographic, a video or an article, but all should include a summary and an impact statement to give context and explain how your results advance your field.

You can communicate your research without seeming like a shameless self-promoter. Science blogging or injecting humour can both help, just remember to link to your latest publication at the end. You don't need to create multiple formats for multiple media channels: you can 'COPE' – Create Once, Publish Everywhere!

2. CHANNEL-HOPPING

The best channels to publicise your work depend on the medium (or media) you are using, the nature of your research and your personality. The following are some of the most popular options.

Kudos (www.growkudos.com)

- helps you explain, enrich and share publications
- great if you have videos, presentations and additional data
- can be a hub for all your publications
- allows you to share your work through other channels and measure the results

Research Gate (www.researchgate.net)

- maintain your profile to showcase your work
- increase your visibility and find collaborators by asking and answering research questions

Twitter (www.twitter.com)

- this will increase your discoverability, even if you have no followers
- 'hashtags' make a topic easily discoverable (e.g. #SfEBES2016)
- 'handles' prompt colleagues, institutions and journals to see and share your tweet (e.g. @Soc_Endo)
- a shared lab account will help you divide the workload
- tweet at different times of day to reach different audiences
- hashtag your research field in your biography, and include a link to a blog or profile
- 'pin' a tweet about your latest paper to fix it at the top of your profile

Blogging (e.g. on www.wordpress.com)

- raise your profile with deeper exploration of specific topics
- guest blogging (writing on established blogs) takes less time and reaches a larger audience (see the Society's blog 'The Endocrine Post' at www.endocrinologyblog.org)

TOP TIPS FOR MAXIMUM VISIBILITY

- Make good use of the staff in your institution who can help you.
- Search for your name, and interact with people who are talking about you.
- Use multimedia to increase the chance of your posts catching people's eyes.
- Create a social media account for your lab, which multiple people can maintain.
- Use hyperlinks behind keywords to push you up search rankings.
- Cater for different languages by translating a summary of your research.
- Seek opportunities: write for *The Endocrinologist*, volunteer for public engagement!
- Front-load titles with keywords to make your content more discoverable.
- Get an ORCID ID (www.orcid.org) so people can easily identify your research.
- Encourage your co-authors to follow all this advice, and the effect will be compounded.

- topics could include 'your typical day', 'awareness days in your field', 'research gaps', 'advice you would have liked when just starting out'
- link your blog to your social media accounts to quickly share articles

Vlogging (e.g. on www.youtube.com)

- video blogging makes it easier to explain complex ideas
- keep the video short, speak clearly, use natural language – and smile!
- include subtitles for those without audio and for non-native English speakers
- use the description box to link to your research

Emails and signatures

- include extra information in your signature: links to your professional and LinkedIn profiles and Kudos, plus your Twitter handle
- add a link to your latest article – someone might click!
- don't distribute PDFs of your papers – if you send a link the downloads will count towards your metrics

Your institution

- maintain your profile on your institution's website
- give a departmental talk about your research, or discuss your article at a journal club
- promote your work on your institution's social media channels

Publishers and the media

- ask the journal that published your article to include it in their marketing
- significant findings may be of interest to the media; work with the press office at your institution, your journal's publisher or the Society for Endocrinology to engage with journalists

3. TRACKING YOUR PROGRESS

You can monitor the impact of your research using article-level metrics found on Kudos or on most journals' article pages. Usage statistics show the number of article views while the Altmetric Attention Score (see example below) allows you to instantly visualise coverage from non-traditional outlets, such as news stories.



All your hard work in promoting your research really should pay off. In the case of Kudos, for example, authors using their tools were found to experience a 23% rise in downloads.

VICTORIA MERRIMAN

Marketing Manager (Publishing), Bioscientifica

TIME FOR TEA? ENCOURAGING A SUPPORT NETWORK AMONG PATIENTS WITH ACROMEGALY

WRITTEN BY JEAN MUNDAY



A light-hearted conversation earlier this year led to a new initiative which has been very well received by our patients with acromegaly.

It all began when colleagues and I commented on how nice it would be if a patient that one of us had just seen could become friends with a lady with acromegaly who lives in the same locality. Because they are of a similar age, we even imagined that they might go for walks and have afternoon tea together! Wondering how we could introduce them to one another, we eventually decided to hold a meeting for a group of patients with acromegaly who attend our clinic.

'Patients often comment that they like the endocrine specialist nurse contact at the hospital, and miss their specialist expertise when it ceases.'

In Portsmouth, these patients are seen in the consultant-led pituitary clinics. Those who need treatment with somatostatin analogues have their initial monthly injections with an endocrine specialist nurse. Once they are on a stable injection dose, we hand over to their practice nurse for ongoing administration. If the practice nurse asks for training, we arrange to meet them and the patient together at their surgery when the next injection is due. Patients often comment that they like the initial monthly endocrine specialist nurse contact at the hospital, and miss their specialist expertise when it ceases.

So, we planned a date and identified a venue for our meeting. Following a search of our electronic database for all patients with acromegaly attending our clinics, we invited 20 to come along.

PLANNING AHEAD

Before the event, the endocrine nurses and specialist registrar met to plan the content of the meeting. We agreed that the main aim was to give patients the chance to meet one another, as many had never met another person with acromegaly. However, we needed some structure, so we included time to update them on innovations and an opportunity to ask questions. For catering purposes, we asked invitees to let us know if they were coming.

Two weeks before the event, we noted that only approximately 50% had replied, so we invited another six patients from our list.

'It was noticeable that most of our patients with acromegaly had never met someone else with the same condition, and how beneficial they found this experience.'

ACTIVITIES ON THE DAY

On the day, 12 patients attended. The specialist registrar and an endocrine specialist nurse ran the event. They demonstrated an app showing patients how they could personally track their care, which many found interesting and informative.

Attendees were also invited to write down anonymous questions that they wished to ask either to the group or to the health professionals. The questions were read out by the doctor or nurse who then answered them, or a group discussion followed. It was thought-provoking for patients to see how others had responded to their diagnosis and treatment. This was the part of the afternoon which many found most beneficial.

LASTING BENEFITS

Interestingly, upon seeing one of the attendees a few weeks later in clinic, I noticed they were calmer about their condition. When I explored this, they mentioned feeling relieved that their symptoms were less severe than those of others they had met, and said they had a new confidence that acromegaly could be managed successfully.

'We are considering which other rare endocrine conditions may benefit from patients meeting one another, and anticipate our next focus will be on those with Cushing's.'

Attendees completed anonymous feedback forms at the end of the event, which showed that 91% felt the group was of great benefit. Everyone said that they would like another similar event to be organised. We noted one specific comment that not all questions had been answered. This was due to time constraints and the inappropriateness of some questions for a group situation; it is something we will try to address at future events.

It was noticeable that most of our patients with acromegaly had never met someone else with the same condition, and how beneficial they found this experience. We therefore have plans to run this group again, inviting the remaining patients with acromegaly from our database. Thereafter we intend to make it an annual event. We are also considering which other rare endocrine conditions may benefit from patients meeting one another, and anticipate our next focus will be on those with Cushing's.

JEAN MUNDAY

Lead Nurse Endocrinology, Queen Alexandra Hospital, Portsmouth

WINNER OF THE INAUGURAL ENDOCRINE NURSE AWARD

The Society's new Endocrine Nurse Award aims to recognise individuals who have demonstrated innovative and successful nurse-led initiatives in the endocrine field that have advanced best practice in research, education or patient care.

QUOTES FROM THE JUDGES:

The Competency Framework for Adult Endocrine Nursing, under the leadership of the candidate, has been recognised and implemented both nationally and internationally with formal publication.

[The Framework has] ... given clear direction as to how endocrine nurses should progress their clinical skills from novice to expert. It is the most significant development in endocrine nursing in the last 5 years.

Ms Kieffer has clearly developed endocrine services locally, but has extended her promotion of endocrine nursing at a national and international level to define the role of an endocrine nurse, and establish competencies. This work has crossed boundaries, leading to international collaboration of endocrine nurses.



Nikki Kieffer.

We are delighted to announce that the winner of the inaugural Award is Veronica (Nikki) Kieffer, Endocrine Nurse Specialist at Leicester Royal Infirmary. Nikki has been chosen for the Award due to her leadership of a project to develop the *Competency Framework for Adult Endocrine Nursing*. Despite strong competition, the judging panel were nearly unanimous in their recommendation of Nikki for the Award.

"Leading the team in developing this unique and valuable tool for adult endocrine nurses was an exciting and rewarding experience, which has seen my 'vision for the future' become a reality," said Nikki.

The Framework, focusing on core knowledge, skills and interventions that are specific to nurses working as adult endocrine nurses, has been published to enhance clinical care received by adults with an endocrine disorder. Nikki was instrumental in its development, and has worked extremely hard to ensure that the 2nd Edition, published in 2015, incorporated four new competencies (see <http://bit.ly/2e12NoB>).

The award will be presented to Nikki after the Endocrine Nurse Award Lecture, which will take place during Endocrine Nurse Update in March 2017 in Birmingham.

If you have a nurse colleague whom you would like to nominate for the 2018 Endocrine Nurse Award, applications are now open until 16 June 2017. For further details, please see <http://bit.ly/2eHAM6z>.

LISA SHEPHERD

NURSE COMMITTEE CHAIR



Christmas is a time of celebration, and this issue of *The Endocrinologist* highlights two timely and exemplary pieces of nursing practice that we should applaud.

First, I am delighted to say that Nikki Kieffer is our winner of the inaugural Endocrine Nurse Award. Nikki has received this honour for her role leading the development and production of the *Competency Framework for Adult Endocrine Nursing*. This ground-breaking piece of work is recognised and utilised by nurse colleagues globally. The Framework is used in practice to recognise, develop, manage and benchmark the knowledge and skills required by adult endocrine specialist nurses.

Don't forget that we are now accepting your nominations for an outstanding nurse to receive the 2018 Endocrine Nurse Award (see <http://bit.ly/2eHAM6z>).

Our second article is from Jean Munday, who tells us about the development of a support network for patients with acromegaly. This

highlights the importance and benefits of peer support by shared experience in rare conditions. It also demonstrates the role of healthcare professionals in the care and follow up of patients with chronic conditions.

We are always keen to hear about anything you have developed or undertake in practice. Please share your ideas and innovations with us in future articles.

On a final note, I wish you all a very Merry Christmas and a Happy New Year, and look forward to seeing you at future Society for Endocrinology events.

LISA SHEPHERD

UEMS: MUCH MORE THAN AN ACRONYM

WRITTEN BY RICHARD QUINTON, GRAHAM ROBERTS, HANS PERRILD & ANTON LUGER



The UEMS (Union Européenne des Médecins Spécialistes) is central to the development of standards for training and education in European endocrinology, and in representing the field at the highest level politically. Here, colleagues from the UEMS Section & Board of Endocrinology (UEMS Endocrinology) update us on the recent review of the training curriculum, and contemplate the impact of Brexit.

FIFA, UEFA ... UEMS: we know what they do (well, the first two at least), but what do the acronyms actually stand for? In fact, all these bodies date from the pre-Anglosphere mid-20th century era when French was still the international language of diplomacy. Otherwise, we would have had IFFA (International Federation of Football Associations), EUFA (European Union of Football Associations) and EUSD (European Union of Specialist Doctors).

The national medical associations of the countries in the EU and European Economic Area (EEA) are full members of the UEMS, with adjacent countries having observer status. Fifty medical disciplines are represented, not including general practice, of which the most important are covered by 39 specialist sections, including 'Endocrinology, diabetes and metabolism'.

THE ROLE OF UEMS

The UEMS represents medical specialists at the level of the European Commission and other EU bodies, and sets standards for the accreditation of training and of continuing medical education. Over the past decade, many of the specialty sections and boards have also established specialty certifying exams, akin to those of the UK Royal Colleges, with endocrinology being set to follow soon. For this reason, we identified a need to revisit our training curriculum.

Members of UEMS Endocrinology Section at their 2015 meeting.



Back in 1991, UEMS Endocrinology produced an outline curriculum under Chapter 6 of the UEMS Charter, known as the 'Leuven/Louvain Document' (<http://uems.dk/files/CHAPTER-6.htm>). It now seems utterly sensible and uncontroversial, simply because so much of it has been implemented (2 years of core training in general internal medicine (GIM), plus 4 years of higher training in endocrinology), but it was truly progressive and radical at a time when the UK and Ireland didn't even have fixed entry and exit points for training.

As an exchange Senior House Officer working in The Netherlands in 1991, Richard Quinton was asked by AJ van der Lely (then a fellow trainee, now President of the European Society of Endocrinology) whether or not he was 'in opleiding' (training). To this, he could only reply that, in the UK, this would only be revealed in the future, depending on whether or not he was eventually appointed to a consultant post! For other countries, the suggestion of a 'common stem' of GIM prior to entry into training proved equally traumatic to die-hard traditionalists.

A NEW REVIEW

In 2016, UEMS Endocrinology established a working group to dust-down the original 1991 curriculum and bring it into the 21st century. We had anticipated that this might be an onerous task, given the passage of time, but we found that it remained scintillatingly relevant.

The revised version maintains the '2+4 year' model (of which, 1 of the 4 years can be spent undertaking related experience, e.g. in a clinical or research laboratory, or in GIM). But it also incorporates advances in disease genetics, diagnostic imaging and multidisciplinary team-working, and it emphasises the centrality of communication/negotiation skills to our specialty. Like the original document, its purpose is as a broad outline, intended to underpin curricula developed by European national bodies or specialist/scientific societies.

THE BREXIT QUESTION

And what of Brexit? Provided the UK remains within the EEA, then nothing changes. However, if it finds itself outside the EEA, then the UK delegate will retain observer status without voting rights, like their Turkish counterpart. However, UK training will still need to conform to the European model, in order to retain mutual specialist training recognition, and the Royal College of Physicians will probably need to continue paying its annual membership fee to the UEMS.

Now, does that sound like a wider metaphor for the post-Brexit UK's relationship with the EU?

RICHARD QUINTON, Newcastle upon Tyne, UK

GRAHAM ROBERTS, Waterford, Ireland

HANS PERRILD, Copenhagen, Denmark

ANTON LUGER, Vienna, Austria

The authors are all National Delegates to UEMS Endocrinology from their home countries. Anton Luger is President of the Endocrinology Section, and Hans Perrild is Executive Committee Member with responsibility for Continuing Professional Development/Continuing Medical Education.

Catch up on the latest news and views via the Society for Endocrinology blog
THE ENDOCRINE POST: www.endocrinologyblog.org

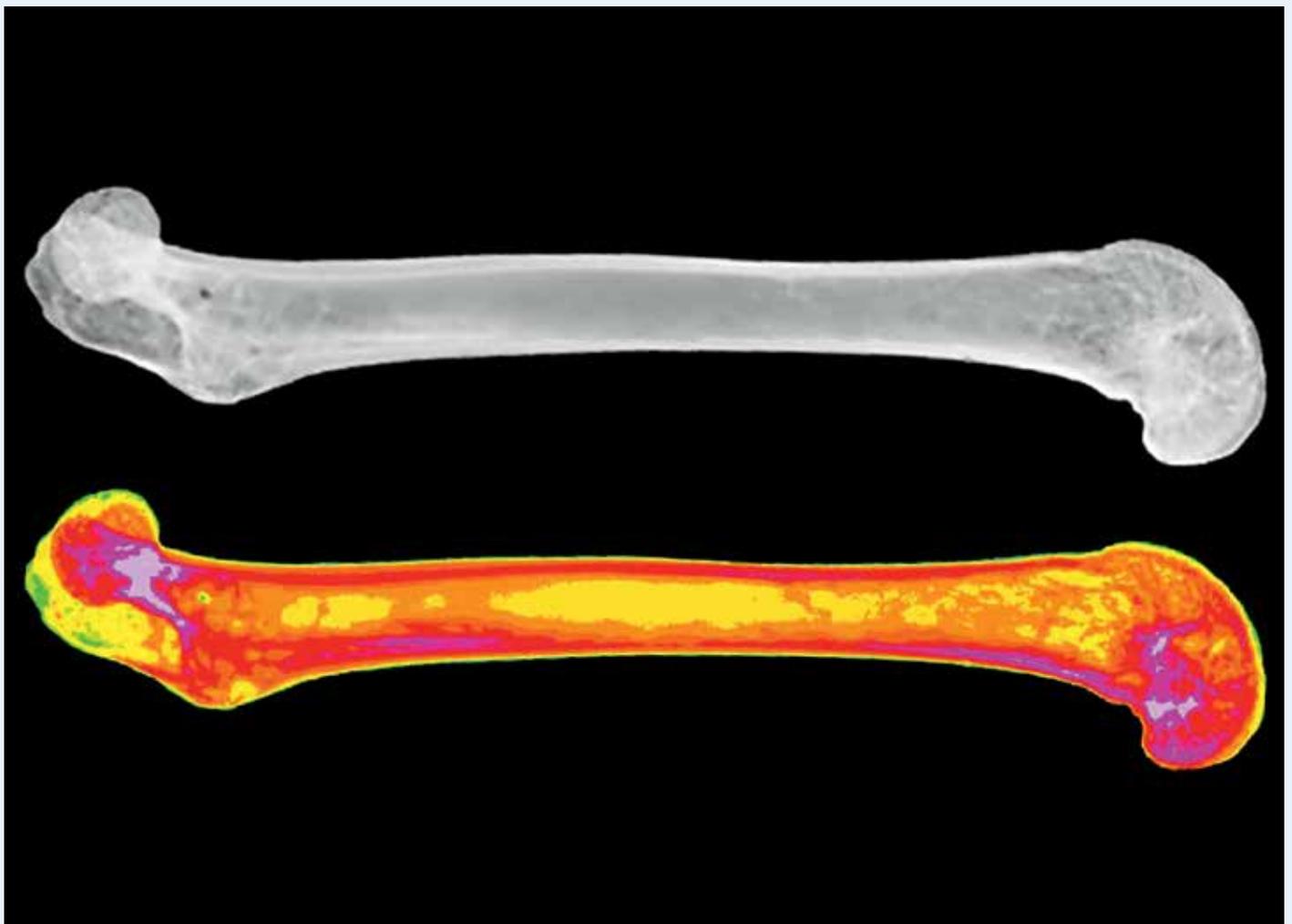
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Here is the latest highlight from our journal Cover Art Competition, showcasing the best images in endocrinology.

COVER IMAGE FROM JOURNAL OF ENDOCRINOLOGY

OCTOBER 2016

Origins of bone and cartilage disease skeletal phenotyping. X-ray microradiography images of a mouse femur. In the pseudo-coloured image, low bone mineral content is shown as green/yellow and high bone mineral content as red/pink. From Freudenthal et al. 2015 *Journal of Endocrinology* **231** R31–R46. Credit: B Freudenthal, J Logan, G Williams, D Bassett (Imperial College London) and P Croucher (Garvan Institute Sydney).



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