Society for Endocrinology

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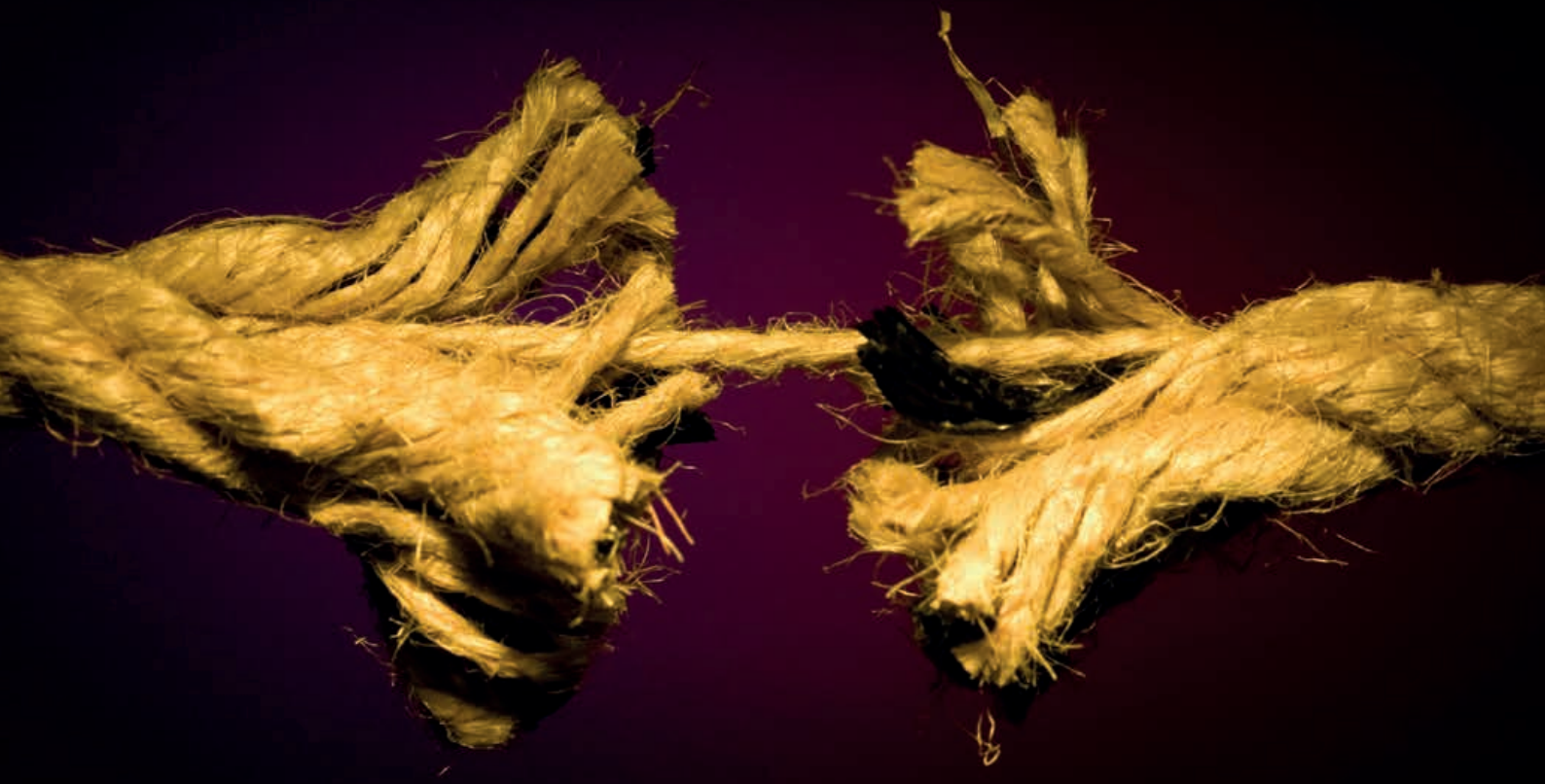
THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

Stress, trauma AND HORMONES



Special features
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A word from THE EDITOR...

Welcome to the autumn issue of *The Endocrinologist*, on the theme of stress and trauma. With the start of the new academic year upon us, this theme feels fitting, ahead of the excitement (and stress!) of preparing for new student intakes and the commencement of teaching. Summer feels long behind us.

At *The Endocrinologist* HQ, we have put together an issue covering many interesting topics. Personal highlights include the insights from Rob Gifford and Thomas O'Leary into **the impact of arduous training on the endocrine system**, focusing on extreme environments encountered during Antarctic expeditions and military training. The themes discussed in that article are echoed in the item contributed by our Editorial Board member John Hough, who discusses **endocrine changes as readouts of overtraining**.

Ashley Cave gives us some interesting tips on **managing our mental health**. Given the multifaceted nature and demands of our roles, this article provides practical advice and a personal anecdote about her own methods of managing her mental health. I know my recent foray into the world of yoga has been beneficial for my own mental health and mindfulness.

I very much enjoyed the opportunity to conduct the issue's **interview with Kevin O'Byrne**. As he studied under the tutelage of many of the greats in reproductive physiology, such as Ernst Knobil, who were making pioneering discoveries that still underpin our knowledge of the reproductive system, it's a fascinating read. Of particular importance is Kevin's advice for ECRs on having confidence in yourself (this is arguably applicable at all career stages), as we can be great self-saboteurs!

Wishing you a wonderful autumn term.

Best wishes

KIM JONAS

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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 WINTER 2024 issue: **14 October 2024**.

Front cover image ©Shutterstock

EXPLORE THE CLINICAL RESOURCE HUB

The Society's Clinical Resource Hub contains a wealth of member-curated resources to help enhance your clinical practice. You can explore materials on subjects such as setting up new clinics, revamping patient communication, best practice in patient-initiated follow up, and much more.

If your clinic has recently introduced measures that have improved your practice or service delivery, make sure you share them on the Hub to help unify endocrine patient care.

Take a look at the Clinical Resource Hub.

Clinical Resource HUB

PUBLISH WITH PURPOSE: SUPPORT YOUR SOCIETY'S JOURNALS

When you publish in one of your Society's journals, you're not just sharing your research – you're investing in the future of endocrinology and supporting your fellow members.

Did you know that the Society's 2024 grant programme was entirely funded by *Journal of Endocrinology*? This means more opportunities for our members to pursue ground-breaking research, advance endocrine education and improve patient care.

And, thanks to profits from *Endocrine-Related Cancer*, the Society's public engagement work was funded for two years, providing non-experts with accurate and reliable information on hormones.

Find out more about your journals.

SOCIETY CALENDAR

26 September 2024
ENDOCRINE GENETIC TESTING
Birmingham, UK

1 October 2024
NATIONAL TRAINING SCHEME FOR THE USE OF RADIOIODINE IN BENIGN THYROID DISEASE 2024
Birmingham, UK

14–15 October 2024
UK JOINT IRISH–UK ENDOCRINE MEETING
Belfast, UK

3 December 2024
REPRODUCTIVE ENDOCRINOLOGY
London, UK

10–12 March 2025
SfE BES 2025
Harrogate, UK

www.endocrinology.org/events for full details

COULD YOU CLAIM FREE MEMBERSHIP OF THE ENDOCRINE SOCIETY?

As part of the Society for Endocrinology's aim to support the global endocrine community, we're offering a new benefit in collaboration with the Endocrine Society. If you're a clinical member in your first year of Higher Specialty Training (Registrar, SpR, or ST3+), you can now claim a complimentary one-year Endocrine Society membership.

This initiative is designed to further the professional development of our early career clinicians, and connect you with a broader network of endocrine specialists worldwide.

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Society for Endocrinology people with

The Society is launching the next generation of real-world data registries. These globally accessible datasets will be enriched by real-time patient information to enhance understanding, inform drug development, optimise patient care and improve patient outcomes.

Your patients will be able to input their data directly into the PeopleWith app, where they can actively monitor their symptoms, track diagnoses and manage medications. This means you will have a more comprehensive overview of patient histories, resulting in more effective treatment plans.

Find out more.

GRANT AND PRIZE DEADLINES

2 October 2024
MEETING GRANT
OUTREACH GRANT
RESEARCH GRANT
TEACHING GRANT
TRAVEL GRANT (including travel to SfE BES 2025)

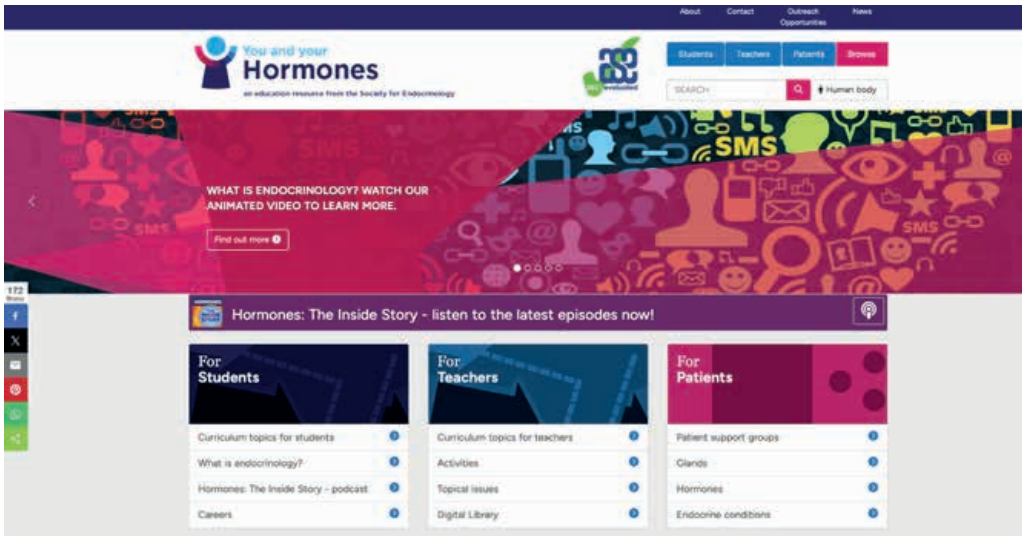
www.endocrinology.org/grants-and-awards for full details of all Society grants and prizes

BECOME A CONTENT EDITOR FOR YOU AND YOUR HORMONES

Are you a scientist with a passion for sharing knowledge and a knack for clear communication? Why not become a Content Editor for our public-facing website, You and Your Hormones?

In a world filled with health misinformation, you can have a positive impact on the public understanding of hormones by translating complex science into accessible, reliable information that educates and empowers patients, students and the public.

Sign up today!



HOT TOPICS

Hot Topics is written by Victoria Chatzimavridou-Grigoriadou, Sophie Clarke, Craig Doig, Edouard Mills, Gareth Nye and Vincent Simpson

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 of the Society website**. *Endocrine Connections*, *Endocrinology, Diabetes & Metabolism Case Reports* and *Endocrine Oncology* are open access and free to all. Publishing in *Endocrine Oncology* is currently free.

JOURNAL OF ENDOCRINOLOGY

ABCC1 constrains metabolic responses to high-fat diet in male mice

Villalobos *et al.* have explored the role of ATP-binding cassette family C member 1 (ABCC1) and its capability to modulate glucocorticoid actions. Using *Abcc1* knockout mice, they showed raised corticosterone levels in skeletal muscle and adipose tissue and enhanced insulin resistance in knockout animals fed a high-fat diet, when compared with wild type controls.

Proteomic and RNA sequencing analyses revealed that knocking out *Abcc1* enhances the transcriptional response to an obesogenic diet in adipose tissue but not in skeletal muscle. Key pathways related to glucose metabolism, particularly OXPHOS machinery and Glut4, are disrupted in both tissues. The findings indicate ABCC1's role in glucose homeostasis, demonstrating diet-dependent effects not linked to altered tissue glucocorticoid concentrations. This research suggests that ABCC1 is crucial for metabolic responses to dietary fat intake, potentially impacting obesity and type 2 diabetes.

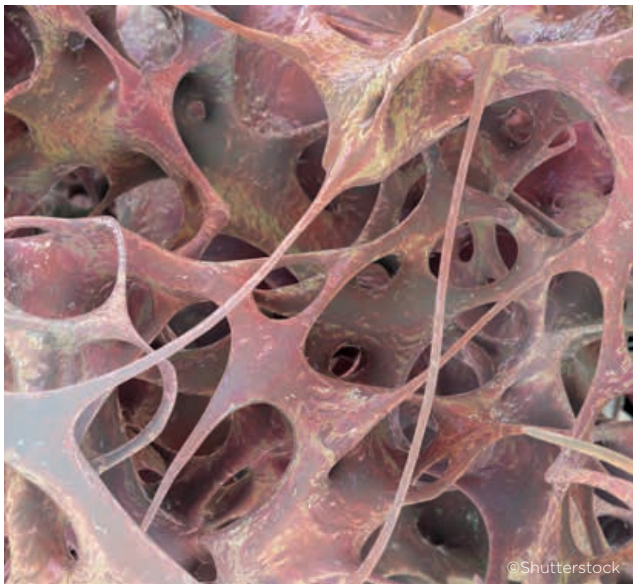
Future studies should investigate the mechanisms by which ABCC1 deficiency amplifies transcriptional responses to a high-fat diet and disrupts glucose metabolism, offering insights into potential therapeutic targets for metabolic diseases.

Read the full article in *Journal of Endocrinology* **262** e240024
https://doi.org/10.1530/JOE-24-0024

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Understanding the progression of postmenopausal osteoporosis

Postmenopausal osteoporosis is a widespread issue globally, but its pathogenesis has remained elusive, due in part to its asymptomatic development. This study by Wang *et al.* has potentially identified a new biomarker to target patients with ongoing postmenopausal osteoporosis: the circular RNA (circRNA) circ_0134120. It appears that this circRNA may be capable of modulating various micro RNAs (miRNAs) and influencing the body.



Comparative analysis in this study, conducted between patients with postmenopausal osteoporosis and healthy controls, revealed distinct expression patterns: specifically, 20 circRNAs displayed a change in their expression. The major novel finding, however, regards uncovering the potential involvement of circ_0134120 in promoting the occurrence and development of postmenopausal osteoporosis through competitive binding with miR-590-5p, facilitating STAT3 expression, and inhibiting the osteogenic differentiation of bone marrow stromal cells. Without this differentiation, bone remodelling cannot progress normally and osteoporosis develops.

This new finding is particularly exciting because of the potential to target this pathway and ultimately prevent postmenopausal osteoporosis for women globally. However, there appear to be potential links to the development of osteoarthritis and other diseases as well.

Read the full article in *Journal of Molecular Endocrinology* **73** e230140
https://doi.org/10.1530/JME-23-0140

ENDOCRINE-RELATED CANCER

Second-line treatments for GH- versus GH&PRL-secreting tumours in acromegaly

Acromegaly primarily results from somatotroph pituitary neuroendocrine tumours (Pit-NETs) secreting growth hormone (GH), with about a quarter of cases involving co-secretion of GH and prolactin (PRL). This latter group presents more aggressively, yet data on the efficacy of GH-lowering therapies are limited.

In a retrospective, multicentre study, Araujo-Castro *et al.* assessed second-line therapies, pasireotide and pegvisomant, for acromegaly. The study included 150 patients who were unresponsive to first-line treatments, 122 having GH Pit-NETs and 28 with GH&PRL Pit-NETs. Among them, 124 were treated with pegvisomant and 49 with pasireotide at any time.

Both drugs effectively normalised insulin-like growth factor-1, with efficacy rates of 71.4% for pasireotide and 81.5% for pegvisomant. Despite the aggressive nature of GH&PRL co-secreting tumours, treatment efficacy did not significantly differ from tumours secreting GH only, though patients with GH&PRL co-secreting tumours required higher doses of pegvisomant. Densely granulated tumours responded less to pasireotide. Pasireotide was also linked to a higher incidence of hyperglycaemia and diabetes when compared with first-generation somatostatin analogues, highlighting the need for careful monitoring.

This study underscores the need for personalised treatment, based on tumour characteristics, offering valuable insights for endocrinologists managing acromegaly.

Read the full article in *Endocrine-Related Cancer* **31** e240043
https://doi.org/10.1530/ERC-24-0043

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CLINICAL ENDOCRINOLOGY

Revised cortisol cut-off in insulin tolerance tests

The gold standard for assessing the hypothalamic-pituitary-adrenal axis is an insulin tolerance test (ITT), which examines the cortisol response to insulin-induced hypoglycaemia. A peak cortisol cut-off of 550nmol/l is regarded as the minimum response for healthy individuals during an ITT. However, this cut-off is based on outdated assays, and risks misdiagnosis of adrenal insufficiency (AI).

In this study, Lazarus *et al*. undertake a retrospective analysis of 300 ITT cortisol responses using the Abbott Architect and Alinity analyser platforms in patients with suspected AI between 2010 and 2022, at a tertiary London centre. Based on the institution's current peak cut-off value of 500nmol, receiver operating characteristic analysis identified a 100.0% sensitivity and 43.6% specificity in correctly diagnosing AI. Using a lower cortisol threshold value of 416nmol/l on the Abbott analyser platform maintained a sensitivity of 100.0% and improved the specificity to 86.7%.

The authors therefore provide evidence to update and lower the Abbott analyser cortisol threshold from 500 to 416nmol/l. Use of this threshold avoids misdiagnosis of AI and subsequent unnecessary glucocorticoid replacement therapy in otherwise healthy patients.

Read the full article in *Clinical Endocrinology*
https://doi.org/10.1111/cen.15074

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Langerhans cell histiocytosis secondary to selpercatinib for metastatic medullary thyroid cancer

Medullary thyroid cancer (MTC) is a rare thyroid cancer arising from the parafollicular cells. It is predominantly caused by mutations in the *RET* proto-oncogene. Cabozantinib and vandetanib are non-selective multi-kinase inhibitors licensed to treat MTC, but they have significant side effects (diarrhoea, hypertension and palmar–plantar erythrodysaesthesia syndrome). Selpercatinib is a selective *RET* kinase inhibitor, currently in phase III trials.

Langerhans cell histiocytosis (LCH) is a rare clonal neoplasm of myeloid dendritic cells not associated with MTC. However, LCH is caused by mutations in the *BRAF* gene downstream of *RET*.

Wu *et al.* report a case of a 22-year-old woman with metastatic MTC who developed LCH while being treated with selpercatinib. She presented with six months of diarrhoea, night sweats, weight loss and hot flushes. Imaging and biopsies confirmed MTC, and she underwent a thyroidectomy followed by selpercatinib treatment, leading to significant symptom improvement and reduced serum calcitonin levels (25,600 to 56ng/l, reference <20 ng/l). After two years of stable disease, bilateral pulmonary nodules were found that rapidly increased in size (4 to 8mm). Lung biopsy was consistent with LCH due to a rare *BRAF* mutation (p.V600_K601>D). She was treated with inhaled steroids, resulting in the improvement of the lung nodules and her symptoms.

This case highlights that tyrosine kinase inhibitors, such as selpercatinib, may paradoxically increase MAPK signalling, potentially leading to secondary neoplasms.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* 23-0079
https://doi.org/10.1530/EDM-23-0079

ENDOCRINE CONNECTIONS

Prader–Willi syndrome: a practical look

This review by Shaikh *et al.* focuses on the management of Prader–Willi Syndrome in a practical and adaptable manner. It will be useful to both paediatric and adult endocrinologists.

The authors have taken care to talk about actual groundwork. This includes the formation of a multidisciplinary team to manage patients with these complex requirements, and undertaking a focused clinical history and examination, presented in a useful and easy-to-digest tabular fashion, for the benefit of clinicians working with these patients (going through esoteric descriptions can make endocrinologists very nervous!). In particular, a thorough review of growth hormone therapy, alongside management of nutrition and puberty, is valuable for adult and paediatric endocrinologists, and can be applied easily.

This article would add confidence to any clinician's repertoire, whilst dealing with a complicated and rare endocrine syndrome.

Read the full article in *Endocrine Connections* **13** e240091
https://doi.org/10.1530/EC-24-0091

ENDOCRINE HIGHLIGHTS

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


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Artemisinins ameliorate PCOS by mediating LONP1–CYP11A1 interaction

Polycystic ovary syndrome (PCOS) is a common endocrine condition. One of its principal features is androgen excess, which can result in hirsutism, scalp alopecia and acne.

Artemisinins are anti-malarial drugs derived from *Artemisia* plants, which have been demonstrated to activate thermogenic adipocytes and improve metabolic health.

Liu and colleagues undertook a series of *in vivo* and *in vitro* studies to explore the impact of artemisinins on androgen excess in PCOS. In rodent models, the artemisinin analogue artemether improved regularity of oestrous cycles, and improved hyperandrogenaemia. Mechanistic studies revealed that artemisinins directly bind to lon peptidase 1 (LONP1) resulting in interaction between LONP1 and CYP11A1. This results in increased LONP1-mediated CYP11A1 degradation, and thus reduces ovarian testosterone synthesis.

Building on this, in women with PCOS (n=19), use of an artemisinin was associated with a reduction in hyperandrogenaemia and an improvement in menstrual cycle regularity.

Taken together, these data suggest that this well-tolerated anti-malarial treatment may offer a novel therapeutic strategy for women with PCOS.

Read the full article in *Science* **384** eadk5382
https://doi.org/10.1126/science.adk5382

Reproductive
ENDOCRINOLOGY

Attend the Society's first REPRODUCTIVE ENDOCRINOLOGY MEETING

This event will bridge the gap between specialty-specific meetings, bringing together experts across multiple fields to provide a masterclass in managing complex reproductive disorders.

Tuesday 3 December 2024

The Hallam Conference Centre, London

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STRESS, TRAUMA AND LATE EFFECTS OF BRAIN TUMOURS

WRITTEN BY HELEN SIMPSON

Imagine you, your child, or someone else you care about is diagnosed with a brain tumour. They may present very unwell, with neurological deficits due to a space-occupying lesion. They may have a suprasellar mass presenting with endocrine issues such as arginine vasopressin deficiency (cranial diabetes insipidus) and hypopituitarism. They may complain of loss of vision. It's all very stressful. And then imagine there is hydrocephalus, ventriculo–peritoneal (VP) shunt insertion, a neurosurgical operation, radiotherapy and possibly chemotherapy. That is all pretty traumatic. We describe this in our service as an acquired brain injury – not a single incident, as in a road traffic accident for example, but multiple and progressive injuries to the brain.

THE ROLE OF THE ENDOCRINOLOGIST

In endocrinology, we are asked to help with the care of people who have undergone treatment for brain tumours, often in childhood.

It is crucial to ask for the field of radiotherapy (especially with the advent of proton beam therapy), in order to know the dose that the hypothalamus, pituitary and thyroid have received. If the hypothalamus/pituitary is not affected, then this cohort is better served in a late effects neuro-oncology service. These are few and far between, especially considering that more and more people live with and beyond a cancer diagnosis. The thyroid is very sensitive to radiation and the neck should be palpated annually in anyone who has had posterior fossa, brain stem or craniospinal irradiation where the thyroid receives some radiotherapy.

Different hormone axes are affected at different doses of radiotherapy (including proton beam therapy) when the hypothalamus/pituitary is in the treatment field:

- Growth hormone defiency can occur after 10–15Gy and occur up to 15 years after treatment. The time to development of deficiency reduces with higher doses, down to around 12 months after 60Gy or more.
- Impact upon follicle-stimulating hormone and luteinising hormone means that precocious puberty can result from doses as low as 15–20Gy.
- Thyrotrophin (TSH) deficiency is less common and predominantly occurs after 30Gy or more.
- Adrenocorticotrophin (ACTH) deficiency is also less common and predominantly occurs after 30Gy or more.

In the case of ACTH, is it important to determine if exogenous glucocorticoid was around at the time of testing for adrenal insufficiency, and that there has been an appropriate test performed, before confirming this important diagnosis. There are issues around assays, cut-offs and dynamic tests used. The glucagon test, for example, performs badly as a test for ACTH/cortisol production. The table shows a suggested testing strategy.

The highest risk of pituitary dysfunction comes in the first 10 years. Our strategy at University College London Hospitals is a dynamic test if growth hormone (GH) is being considered 6–12 months after completion of treatment, then a 9am blood test annually for 10 years unless the clinical picture changes. GH testing frequency is harder to determine: my strategy is roughly 5 years for two dynamic tests as determined by adult GH deficiency assessment (AGDHA; if over 25) and discussion with the patient. While GH is not licensed in active malignancy, to date there are no safety concerns in this cohort. The main risk is of type 2 diabetes in those with additional risk factors.

NEUROLOGICAL IMPACT

As well as affecting hormone production, radiotherapy can affect neurones and dendritic connections, and result in issues with neurocognitive function, or issues with higher executive functions, such as learning, memory and processing speed of the brain. This is more apparent the younger the person is having radiotherapy, and is associated with the volume of brain affected, and the site of neurosurgery. For example, a cohort of young people in our care have had whole brain irradiation (e.g. for medulloblastoma), receiving 40Gy, and have significant early memory loss in their 30–40s. Memory loss can make it difficult to manage aspects of hormone replacement, in particular desmopressin and glucocorticoid replacement, and remembering

Table. Suggested strategy for endocrine testing. FSH, follicle-stimulating hormone; LH, luteinising hormone.

Serum pituitary basal hormone levels	• Insulin-like growth factor-I is not diagnostic for GH deficiency in adults • Follicular phase LH and FSH, oestradiol if menstruating • LH FSH oestradiol if not menstruating (no need to repeat once on oestrogen replacement) • 9am testosterone in men • TSH/free thyroxine • 9am cortisol
Hormone stimulation tests	• Short synacthen test • Insulin tolerance test (ITT) to assess GH/cortisol reserve • Glucagon stimulation test or ITT to assess GH status – only if considering GH replacement
Additional useful investigations if concerned about diabetes insipidus (not a late effect)	• Plasma and urine osmolarities • Water deprivation test

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sick day rules. Radiotherapy can affect blood vessels in the brain; the risk of stroke increases, and rises further after about 20 years. We don't know the mechanism for this or how to manage it. It is important to focus on healthy eating and exercise, and monitoring other cardiovascular risk factors such as lipids, glycated haemoglobin and blood pressure. **St Jude's CVS Risk Calculator** may also be helpful in decision making.

Neurosurgery can be life-saving. You don't need me to describe how this is traumatic to the brain. Hydrocephalus, often the first presentation of a primary brain tumour, causes pressure in the brain, managed with a VP shunt or Omyaya reservoir. Shunts can block, malfunction and, rarely, get infected, so needing to be removed. An often forgotten, important part of care for this patient group is ensuring that they are known to a hydrocephalus service, so they can have a shunt check as needed.

How all of this can affect people in terms of neurocognitive function and also mental health spans a huge spectrum. It is common to see young people with anxiety, and there are a number of people with mental health diagnoses, such as psychosis and severe depression. Referrals for talking therapies, neuropsychology or psychiatry should be considered.

IDENTIFYING SUPPORT SERVICES

One of the challenging aspects of care is linking to services that can support this cohort, as services are not commissioned, and many are community-based and can be difficult to access, or are non-existent. Part of the jigsaw that is helpful for patients is a documented educational assessment, documenting if the young person has a learning disability, and ensuring young people are linked with adult learning disability teams prior to transition to adult services. Patient support groups such as Trekstock, Macmillan, Ellen MacArthur Trust, Children's Cancer and Leukaemia Group, Headway, Success and Brainstrust can offer support. It is important to know if there is a lasting power of attorney for health in place for those with significant brain injury, and Citizens Advice and local Council adult learning disability teams can be a source of information for parents and carers. Macmillan has support to navigate the benefits system.

Neurocognitive function testing should be considered where these may be a concern, as strategies can be offered linking to occupational therapy and vocational therapy. Young people may need support navigating the education system and going to university, along with support in the workplace.

Fatigue is a very common. It is rarely related to endocrine deficits if they are appropriately replaced. It is usually related to the acquired brain injury itself affecting capacity of neurocognitive function. Links with neurology and brain injury teams can be helpful to access support and discuss strategies, such as pacing activities and good sleep patterns. Some people have access to fatigue management services run by occupational therapy and, if so, a referral here can be helpful.

There is a lot to consider – stress and trauma coming from both tumours and treatments. Endocrine deficits should not be missed, and we should screen for long term impacts of treatments appropriately and pragmatically. Multidisciplinary working is key, with non-medical interventions often being the most important for quality of life. There remains a gap between services needed and what is available.

HELEN SIMPSON
Deputy Clinical Lead Diabetes and Endocrinology,
UCLH NHS Foundation Trust

FURTHER READING

Children's Cancer and Leukaemia Group *Late Effects Factsheets* www.cclg.org.uk/publications/late-effect-factsheets.
Gebauer J *et al.* 2019 *Endocrine Reviews* https://doi.org/10.1210/er.2018-00092.
Headway *Fatigue after Brain Injury* www.headway.org.uk/about-brain-injury/individuals/effects-of-brain-injury/fatigue.
International Late Effects of Childhood Cancer Guideline Harmonization Group www.ighg.org.
Late Effects Special Edition 2022–2023 *Endocrine Connections* https://ec.bioscientifica.com/page/lateeffects/late-effects-special-issue.
Macmillan *Endocrine Late Effects Guide* www.macmillan.org.uk/healthcare-professionals/news-and-resources/guides/endocrine-late-effects-guide.
Office of the Public Guardian *Lasting Power of Attorney* www.gov.uk/power-of-attorney.
Stochholm K & Kiess W 2018 *Clinical Endocrinology* https://doi.org/10.1111/cen.13502.

ENDOCRINE IMPACT OF ARDUOUS EXERCISE IN WOMEN AND MEN

WRITTEN BY ROBERT M GIFFORD AND THOMAS J O'LEARY

This summer marks the 40th anniversary of the first women's Olympic marathon. Since then, women have been closing the gap with men in the results tables of ultra-endurance events, such as the Marathon des Sables, Ultra Trail du Mont Blanc and the Barkley marathons. Women have also pioneered extreme adventurous and occupational endeavours which, until recently, were the preserve of men. These include physically demanding combat roles in the military, polar traverse expeditions and ultra-endurance rowing.

Intense and sustained exercise can lead to an energy deficit (energy expenditure higher than dietary energy intake), which activates the hypothalamic-pituitary-adrenal (HPA) axis to increase circulating glucocorticoid levels and improve substrate availability to tissues. This adaptive response is fundamental to survival. However, as a high proportion of available energy is apportioned to locomotion, prolonged downregulation of less essential processes may be pathological, e.g. suppressed reproductive function.[1] The suppression of reproductive function is an adaptive response to stress, with the aim of reducing likelihood of conception during times when a successful live birth is less probable, but the subsequent suppression of sex steroid hormones has other effects that can be harmful to health (e.g. musculoskeletal) and aspects of physical and cognitive performance.

'Studies comparing metabolic function during prolonged exercise have demonstrated a sexually dimorphic pattern of adaptation.'

LESSONS FROM THE ANTARCTIC

Polar ski touring is an example of vigorous physical activity and energy deficit with high 'stationarity', i.e. a day-to-day routine which remains largely unchanged over several weeks. During the first all-female Antarctic traverse expedition, six women completed the 1700km land mass traverse in 62 days (the largest team to ever do so of any gender, see images) and demonstrated preserved pituitary gonadotroph function[2] and bone density,[3] despite a mean 9kg weight loss and marked activation of the HPA axis.

We recently studied a larger Antarctic expedition of six men and three women. In this cohort, greater loss of fat mass and fat-free mass was seen among men than among women,[4] a separation which became apparent after around 30 days of activity. This finding was consistent with some evidence from military cohorts that women better protect fat-free mass in multi-stressor environments than do men.

Energy deficits are a major contributing factor to fat-free mass loss. Women typically have lower body size than men – which contributes significantly to the difference in energy cost in locomotive tasks. This means they may also find it easier than men to maintain an energy balance in environments when energy intake is restricted by logistical challenges (e.g. the amount of food you can carry or the time available for eating).

Salivary steroid levels in this mixed expedition suggested greater activation of the HPA axis among women than in men, and more suppression of testosterone levels among men (unpublished data). Studies comparing metabolic function during prolonged exercise have demonstrated a sexually dimorphic pattern of adaptation, with women preferentially utilising more fat than men.[5] Storing and utilising more adipose tissue allows women to preserve lean mass during an energy deficit, mitigating maladaptive endocrine effects. This sex-specific difference appears to become more relevant as exercise is sustained.

MILITARY TRAINING

While women may compare favourably to men in many adaptations to an energy deficit, they demonstrate higher rates of pertinent adverse outcomes in settings that expose them to multiple concurrent stressors. For example,

The six soldiers of the Ice Maiden expedition at the South Pole; the first all-female team to ski across Antarctica using muscle power alone. Crown Copyright

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The Ice Maiden expedition traversed 1,700km in 62 days. Crown Copyright

during arduous military training, women experience higher rates of stress fracture than men.[6]

It is difficult to compare male and female reproductive outcomes, but rates of ovarian dysfunction are high during military training.[7] Female reproductive dysfunction during military training is associated with maladaptive metabolic responses, possibly driven by heightened average glucocorticoid exposure.[8] We conducted a study of HPA axis and pituitary gonadotroph responses to 29 weeks of basic military training in nine men and 34 women. The HPA axis was markedly more activated among women than in men, with evidence of greater suppression of gonadotroph function (unpublished data).

It is difficult to precisely delineate the individual stressors which contribute to stressful circumstances such as military training. In this study, men demonstrated more energy deficit than women,[9] so it is perhaps less likely that negative energy balance was a major contributing factor. Other stressors which could plausibly explain these findings include sleep deprivation, the enforced nature of training (an 'external locus of control'), hydration status and psychological coping strategies. Altered sleep has a potentiating effect on reactivity of the HPA axis[10] and is commonly reported during military training, with greater HPA axis responsiveness seen in women under sleep deprivation.[11] Dehydration leads to co-activation of HPA axis and arginine vasopressin in a sex-specific manner.[12] Whilst the athlete literature highlights energy deficits as having the major contributing role in impaired reproductive function in female athletes, women undergoing arduous multi-stressor training or expeditions may experience reproductive dysfunction as a result of a number of individual factors or the combination of these factors.

FUTURE STUDIES

The next steps are to better understand individual observations in environments that involve multiple concurrent stressors (for instance during military or police employment), and to define which factors contribute to maladaptive metabolic and endocrine responses. Both basic science and clinical interventional approaches are needed, to determine how factors may affect the HPA axis in a sex-specific manner, contributing to female reproductive dysfunction and associated pathologies. This will allow the development and trialling of mitigating solutions which will optimise female integration into these environments, to capitalise on increased diversity.

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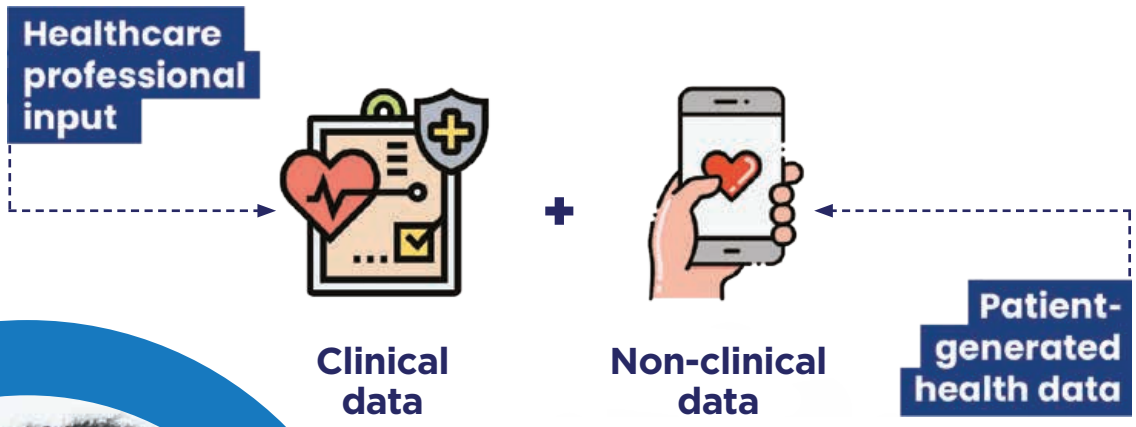

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OVERTRAINING AND THE ENDOCRINE SYSTEM
CAN HORMONES INDICATE OVERTRAINING?

WRITTEN BY JOHN HOUGH

In any successful exercise training programme, there is a need to include stress, adaptation and recovery phases. In order to help you to avoid 'overtraining' – an action that can lead to extreme fatigue, where recovery can take weeks to years to occur[1] – there is a need to balance the stress and recovery phases.

PREVALENCE OF OVERTRAINING

Even if you exercise regularly, it is difficult to know what your risk may be of overtraining. We do know that high level athletes are more likely to suffer from overtraining due to their intense training demands, with studies showing that between 30%[2] and 60%[3] of athletes experience signs of overtraining. But research that specifically examines how often the average person experiences overtraining is scarce.

The symptoms of overtraining are varied and inconsistent, which therefore makes it difficult to diagnose, but symptoms that are commonly reported include persistent fatigue, decreased performance, mood disturbances and disturbed sleep.[1] There is some indication that overtraining can lead to altered hormonal activity. This may be useful, as we could use an endocrine biomarker to highlight the incidence of overtraining.

'The hormonal changes associated with overtraining, including blunted cortisol and reduced anabolic hormones in response to exercise stress tests, highlight the importance of balanced training and recovery.'

HORMONAL ALTERATIONS WITH OVERTRAINING?

The hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes have been reported to be affected by overtraining. Measurement of the hormone cortisol or its precursor adrenocorticotrophic hormone (ACTH) provides an indicator of HPA activity. We know that both cortisol and ACTH are released when we complete moderate or intense exercise stress.[4] The increases in HPA axis hormones from exercise-related stress are typically short-lived; they usually return to baseline concentrations within an hour[4] after exercise. Anyone who frequently trains at a high level will therefore repeatedly experience elevated ACTH and cortisol levels due to exercise-related stress.

Work from our laboratory has found that cortisol responses to a high intensity, 30-minute cycle exercise stress test are lowered following a short period (11 days) of intensified exercise.[5] This observation, alongside findings from other research,[6] suggests that, during periods of overtraining, both ACTH and cortisol concentrations in our blood may be decreased in response to a stressful event – such as exercise.

The response of the HPG axis to a stressor also appears to be blunted following periods of intensified training (i.e. overtraining). In several studies, our laboratory has reported lowered exercise-induced testosterone in blood and saliva when compared before and after intensified training stress periods of 9–12 days.[5,7,8] Indeed, a lowered testosterone concentration has previously been reported during periods of intensified training, e.g. training camps or, indeed, over years of exercise training.[9] As testosterone holds a crucial role in muscle repair and growth, a deficiency can result in impaired recovery.

MECHANISMS BEHIND THE HORMONAL CHANGES

The blunted cortisol alterations seen with overtraining may be a protective mechanism for the body, when it is repeatedly exposed to increased cortisol levels. It is likely that a desensitisation of the adrenal glands or a dysfunctional hypothalamus or pituitary gland are the possible cause of the reduction in cortisol. During periods of chronic stress exposure, a suggested cortisol resistance can occur, leading to a lowered cortisol response to stress due to an interplay between the nervous, endocrine and immune systems.[10]

The lowered testosterone responses seen in periods of overtraining could be due to an exposure to regular elevations of exercise-induced cortisol from the daily training sessions. Cortisol is known to interfere with testosterone's androgen receptor binding.[11] It is also possible that increased testicular vascular resistance leads to a lowering of blood flow and therefore a blunting of testosterone in blood. In addition, from work in an animal model,[12] it appears that the pro-dynorphin (*Pdyn*) gene is upregulated with a period of intensive exercise. This gene inhibits gonadotrophin-releasing hormone and luteinising hormone, which therefore may lead to a reduced testosterone response seen during overtraining.

To conclude, overtraining is a complex syndrome, which can impair athletic performance and health. The hormonal changes associated with overtraining, including blunted cortisol and reduced anabolic hormones in response to exercise stress tests, highlight the importance of balanced training and recovery.

This work also suggests that hormonal biomarkers in response to an exercise stress test may be useful measures to reduce the risk of overtraining. By understanding these hormonal mechanisms and implementing strategies to prevent overtraining, athletes can optimise their performance while safeguarding their health.

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ADRENAL INSUFFICIENCY AND STRESS:

WE NEED EVIDENCE FOR SICK DAY RULES

WRITTEN BY ZIN HTUT, NIAMH MARTIN AND KARIM MEERAN

The mortality rate in patients with adrenal insufficiency is higher than in the general population, mainly because of an increased risk of cardiovascular death. This may be due to excess steroid exposure, or replacement regimens that are uncoupled from the normal physiological cortisol profile.[1]

Adrenal insufficiency requires careful management to prevent life-threatening adrenal crises. 'Sick day rules' recommend increased glucocorticoid doses during physiological stress, such as illness or surgery. However, the evidence supporting the optimal glucocorticoid dose and duration is lacking. A better understanding of stress effects on the hypothalamic-pituitary-adrenal (HPA) axis is needed to inform the development of future guidelines. Additionally, the evolutionary advantage of elevated serum cortisol levels during stress may no longer apply in a world with antibiotics, vaccinations and intensive care units. Simply doubling or tripling the dose of hydrocortisone when the patient may have been exposed to minor 'stress' may be harmful, particularly if this is frequent.

The control of the HPA axis is poorly understood. While there are circadian and ultradian rhythms, the exact mechanism by which the hypothalamus modulates cortisol levels is unknown.[1] Corticotrophin-releasing hormone (CRH) stimulates adrenocorticotrophin (ACTH), which then stimulates cortisol, with negative feedback at the level of the hypothalamus and pituitary. The regulation of hypothalamic CRH release is complex, involving stimulatory and inhibitory neural networks.

STRESS RESPONSE VARIABILITY

It is believed that 'stress' may cause an increase in activity of the HPA axis, although there is an extremely wide inter-individual variation in HPA responses to similar stress. Deconvoluted data of individual patients show enormous variability.[2] Ten 24-hour serum cortisol profiles from adult females indicate that the adrenal gland produces cortisol in distinct bursts, superimposed on a circadian rhythm. Despite this episodic secretion, the overall cortisol concentration remains continuous but highly variable and unpredictable in each individual (Figure).

" 'Sick day rules' recommend increased glucocorticoid doses during physiological stress, such as illness or surgery. However, the evidence supporting the optimal glucocorticoid dose and duration is lacking."

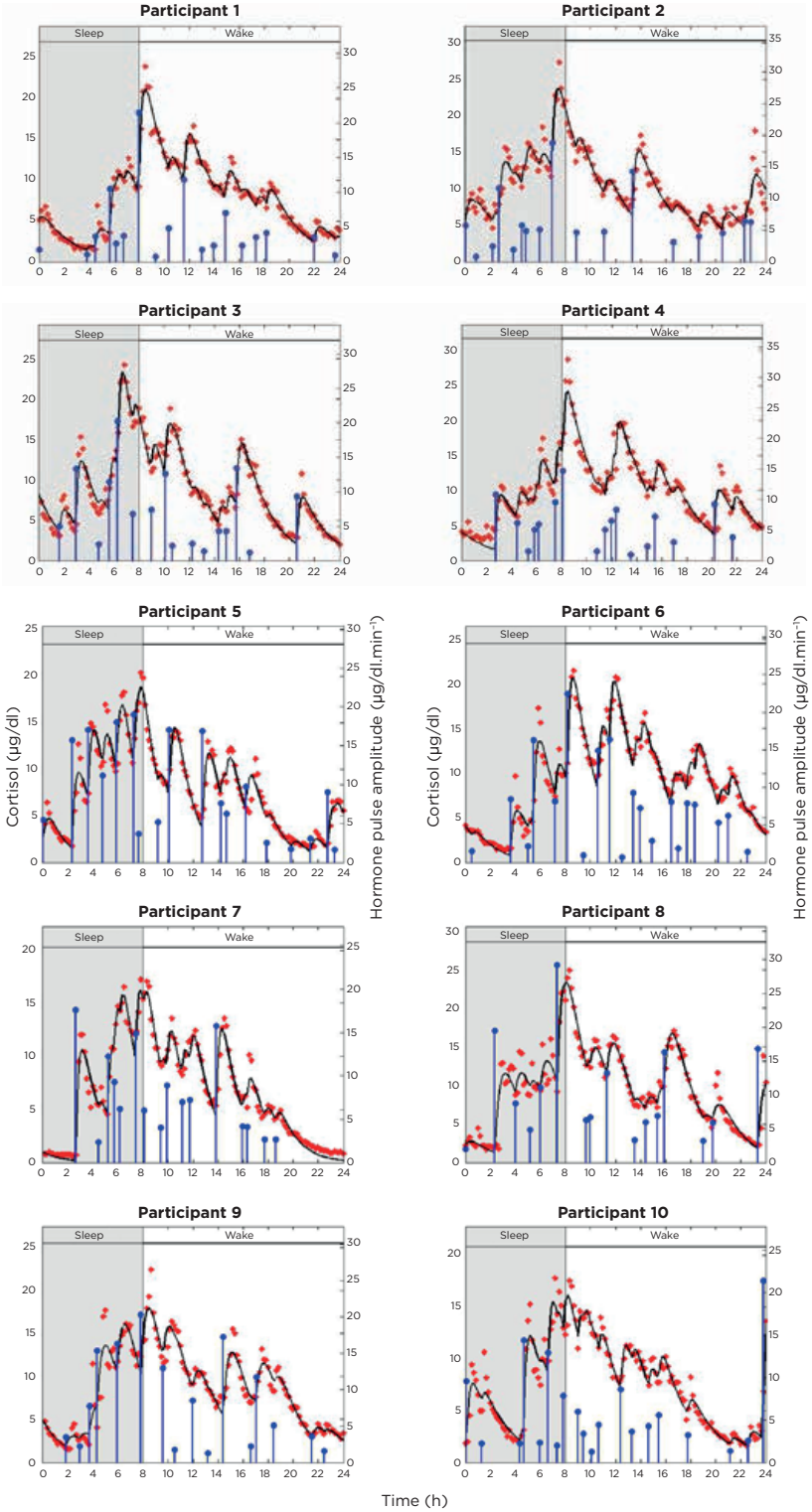

Figure. 24-hour serum cortisol profile in 10 individuals demonstrating wide variations between individuals. Reproduced under Creative Commons Attribution License from Faghih *et al.*[2] ©2014 The Authors.

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The 'sick day rules' were suggested following the publication, in 1968, of the effects of surgery on cortisol levels in 40 individuals who were undergoing surgical procedures, such as gastrointestinal surgery, hysterectomy or hip osteotomy.[3] The study noted wide variation in cortisol responses to the same surgery among different individuals, although the individual data were not provided.

Recent data show wide variation in cortisol responses among 93 euadrenal patients undergoing elective surgery.[4] Despite the physiological stress of a cholecystectomy, some individuals demonstrated almost no rise in cortisol. The study categorised surgeries by severity: major/major+ (n=37), moderate (n=33) and minor (n=23). Peak serum cortisol concentrations ranged from 272 to 1066nmol/l after minor surgery and from 375 to 1452nmol/l after major surgery.

Surprisingly, ACTH levels are not responsible for the peri-operative rise in cortisol. Following cardiac surgery, there is a significant surge in both ACTH and cortisol levels. Even after ACTH levels return to baseline, cortisol remains elevated, which suppresses ACTH. This suggests an increase in adrenal sensitivity to ACTH.[5]

'Understanding what type of 'stress' activates the HPA axis will help develop a more nuanced approach to sick day rules.'

GLUCOCORTICOID DOSING DURING STRESS

Although we prescribe double or triple doses of glucocorticoids during times of stress,[6] evidence of benefit is unclear, and it may be harmful in some cases. The interpretation of stress is highly variable. Evidence is difficult to obtain because, if there is a benefit, withholding increased glucocorticoids could be harmful. Understanding what type of 'stress' activates the HPA axis will help develop a more nuanced approach to sick day rules. Using extra glucocorticoids during sepsis might be harmful, given their immunosuppressive effects.[7]

A retrospective study by Hahner *et al.* documented 384 adrenal crises over 6092 patient-years, with an incidence rate of 6.3 crises per 100 patient-years, mainly triggered by gastrointestinal infections and fever. The incidence was unaffected by educational status, body mass index, glucocorticoid dose, dehydroepiandrosterone treatment, age at diagnosis, hypogonadism, hypothyroidism, or growth hormone deficiency.[8] A follow-up prospective study involving 423 patients found a high prevalence of adrenal crises even among educated patients, with no other significant associations other than a history of crises.[9] These studies suggest that patient knowledge and understanding of sick day rules have not improved patient outcomes.

The suggestion that steroid doses are doubled or tripled should refer to patients on replacement doses of prednisolone (2–4mg) or hydrocortisone (10mg+5mg+2.5mg). However, patients on higher, immunosuppressive doses for rheumatological conditions might double their prednisolone from 20 to 40mg, even though 20mg is already well above a typical stress dose.[10]

Others report that patients following sick day rules have better outcomes when they develop sepsis, but it's important to understand that recovery associated with glucocorticoid use doesn't necessarily mean that the glucocorticoid caused the improvement. Thus, septic hypotensive patients typically receive antibiotics and fluids first, and any progress seen after steroids might be due to these initial treatments or improved fluid management, rather than the steroids. If there is no immediate response to steroids, additional doses are given, and any eventual improvement is often mistakenly attributed to the glucocorticoid. This potential bias should be considered before attributing the improvement to the hydrocortisone. While many believe sick day rules are beneficial, there is limited evidence beyond self-assessment questionnaires, and publications often lack data on adrenal crisis frequency, hospitalisations and mortality rates.[11]

'Future studies should focus on optimising dosing strategies and using technology for real-time monitoring of cortisol levels to improve patient management during stress.'

OPTIMISING DOSING STRATEGIES

Glucocorticoid dosing recommendations for adrenal insufficiency vary widely, indicating a lack of consensus on optimal strategies and underscoring the need for robust evidence to standardise practice. Current sick day rules, based on observational studies, physiological data and consensus, are widely recommended, but have not been proven to reduce the incidence of adrenal crises. Long term supraphysiological glucocorticoid doses may lead to weight gain, metabolic syndrome, muscle wasting and impaired immune response, and contribute to the increased mortality that we know occurs due to cardiovascular disease. The absence of high quality randomised controlled trials and standardised dosing protocols highlights the need for more research. Future studies should focus on optimising dosing strategies and using technology for real-time monitoring of cortisol levels to improve patient management during stress.[12]

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GH REPLACEMENT FOR TRAUMATIC BRAIN INJURY AND SUBARACHNOID HAEMORRHAGE

WRITTEN BY KATHRYN KINSELLA

Traumatic brain injury (TBI) and subarachnoid haemorrhage (SAH) are a significant cause of disability and mortality worldwide, often leading to long term physical, cognitive and emotional impairments. Despite advances in medical science, effective treatments for TBI and SAH remain limited. However, recent research suggests that growth hormone (GH) therapy could play a pivotal role in the recovery and rehabilitation of these patients when they have been found to have pituitary dysfunction. This article explores how GH replacement benefits patients with TBI and SAH, emphasising its impact on neuroprotection, neurodegeneration, cognitive function and overall quality of life.

NEUROPROTECTION AND NEUROREGENERATION

One of the primary benefits of GH therapy in cases of TBI and SAH is its role in neuroprotection and neuroregeneration. GH has been demonstrated to promote the survival of neurones and to reduce cell death following brain injury. The exact mechanism by which GH preserves neuronal integrity after injury is not fully understood.[1] GH has been found to exert its neuroprotective effects through the stimulation of insulin-like growth factor-1 (IGF-1), which is crucial for neuronal survival and plasticity. Montivero *et al.* advise that IGF-1 helps in reducing inflammation and oxidative stress,[2] both of which are significant contributors to neuronal damage after TBI and SAH.

Additionally, GH and IGF-1 enhance neurogenesis, particularly in the hippocampus, a region critical for memory and learning. Studies have demonstrated that GH administration can increase the proliferation of neural stem cells and their differentiation into functional neurones.[3] This neuroregenerative capacity is vital for restoring lost cognitive functions and improving brain plasticity, thereby aiding recovery in patients with TBI and SAH.

ENHANCEMENT OF COGNITIVE FUNCTION

Cognitive impairments are common among patients with TBI and SAH, affecting memory, attention, executive function and processing speed. GH therapy has shown promise in mitigating these cognitive deficits. The hippocampus, highly involved in cognitive processes, is particularly sensitive to GH and IGF-1. By promoting hippocampal neurogenesis and synaptic plasticity, GH therapy can enhance learning and memory functions.

Clinical studies have indicated improvements in cognitive performance among patients with TBI and SAH who are receiving GH therapy, where they have been diagnosed with GH deficiency. These improvements include better memory recall, increased attention span and enhanced problem-solving abilities. Such cognitive enhancements are crucial for the reintegration of individuals with TBI and SAH into daily life and their ability to regain independence.

'GH administration can increase the proliferation of neural stem cells and their differentiation into functional neurones.'

PHYSICAL REHABILITATION AND MOTOR FUNCTION

Motor function impairments, including weakness, co-ordination problems and spasticity, are prevalent in people with TBI and SAH. GH can facilitate physical rehabilitation by improving muscle strength and co-ordination. GH influences muscle metabolism, increasing muscle mass and reducing fat accumulation, which is essential for patients who often experience muscle atrophy due to immobility.

Furthermore, GH has been associated with improved motor skills through its effects on the central nervous system. By promoting the repair of motor pathways and enhancing synaptic transmission, GH therapy can lead to better motor control and co-ordination. This improvement in physical abilities significantly contributes to the overall rehabilitation process and the patients' quality of life.

'Ultimately, the benefits of GH therapy for patients with TBI and SAH culminate in an enhanced quality of life.'

EMOTIONAL AND PSYCHOLOGICAL BENEFITS

The emotional and psychological well-being of patients with TBI and SAH is often compromised, with many experiencing depression, anxiety and mood swings. GH therapy has been linked to improvements in mood and emotional stability.

Patients undergoing GH therapy have reported reduced symptoms of depression and anxiety, better emotional regulation, and an overall improvement in their sense of well-being. These psychological benefits are critical for the holistic recovery of individuals with TBI and SAH, as emotional health significantly impacts their motivation and engagement in rehabilitation programmes.

QUALITY OF LIFE

Ultimately, the benefits of GH therapy for patients with TBI and SAH culminate in an enhanced quality of life. By addressing the multifaceted impairments caused by TBI and SAH – cognitive, physical, and emotional – GH therapy supports a more comprehensive recovery. Patients experience better cognitive function, improved physical capabilities and greater emotional stability, enabling them to reintegrate into their communities and lead more fulfilling lives.

ACCESS TO TREATMENT

The information above demonstrates the immense impact of GH treatment on the well-being of patients after TBI/SAH. The issue appears to lie with identification of pituitary dysfunction and access to treatment. Numerous studies have supported the positive effects of GH replacement in this cohort of patients but, ultimately, how are these patients to be identified: who is responsible for screening?

Post-traumatic hypopituitarism occurs frequently and is under-diagnosed and under-treated. Lack of clear referral pathways mean that patients do not get referred and access to treatment varies according to local services and experience of local healthcare providers. Barriers to implementing a service for these patients tend to centre on lack of education, lack of clear referral pathways and lack of resources. A comprehensive study by Giritharan *et al.* concluded that although it is recommended that all SAH survivors be

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screened for endocrine dysfunction, this may not be always be feasible and has a substantial impact on resources.[4]

Combating these issues should be addressed collaboratively by the wider endocrine community to help evolve and develop future services and care for these patients. The implementation of clear referral pathways and embedding education into training programmes will help the plight of this patient group.

IN CONCLUSION

GH therapy offers substantial benefits for patients with TBI and SAH. Its neuroprotective and neuroregenerative properties, combined with its positive impact on cognitive function, physical rehabilitation and emotional well-being, make GH a promising treatment for enhancing the recovery and quality of life of those with TBI and SAH. As research continues to evolve, the integration of GH therapy into standard TBI and SAH treatment protocols holds the potential to transform the rehabilitation landscape for millions of individuals affected by this debilitating condition.

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INTERVIEW

An interview with… KEVIN O'BYRNE A PASSION FOR THE GnRH PULSE GENERATOR

Kevin O'Byrne is Professor of Reproductive Neuroendocrinology in the Department of Women and Children's Health at King's College London. Here, he tells us about his career journey so far, his fascination with the mechanisms of pulsatile gonadotrophin release, and his advice for you if you are just starting out in endocrinology.

Tell us about the focus of your research

My passion in science is the gonadotrophin-releasing hormone (GnRH) pulse generator: the amazing neural oscillator in your hypothalamus that eventuates in the pulsatile release of GnRH, which, in turn, drives the pulsatile release of the gonadotrophic hormones, luteinising hormone (LH) and follicle-stimulating hormone (FSH), to control the gonads.

This field was transformed by the discovery, 20 years ago, of kisspeptin, and the realisation that the kisspeptin neurones in the hypothalamus are the major component of this neural construct, diverting attention away from the GnRH neurones per se as the pacemaker. To be part of that was so much fun.

How has your career journey brought you to this point?

As an undergraduate studying mostly respiratory physiology, my attention was captivated by Richard Dyball's visit to Chelsea College, as part of a tiny reproductive physiology module, to demonstrate the milk ejection reflex in the rat model. Off I went to Bristol to do my PhD with Alastair Summerlee in the very department at the epicentre of that research. I was surrounded by all the main players – astonishing.

I was then invited to join Dennis Lincoln at the MRC Reproductive Sciences Unit in Edinburgh, to use my *in vivo* electrophysiology skills to study the multi-unit activity (MUA) volleys, the electrophysiological correlate of the GnRH pulse generator, in the exotic marmoset monkey. That was a complete failure, so I decided to join Ernst Knobil, in Houston, TX, USA, who discovered the MUA volleys in the rhesus monkey.

After six amazing years in Texas, I decided to return to the UK, because I was concerned about how difficult it was to get a tenure track position in the USA. King's College London seemed like an interesting place, so I joined the Anatomy Department in 1994 and have studied the GnRH pulse generator ever since.

How have technological advances shaped your research?

I have always felt that technology is absolutely key to advancement in science, so I have always wanted the latest 'toys' applicable to *in vivo* work in freely behaving animals.

Naturally, the mouse, which we all take for granted, revolutionised our capabilities. The exquisite activation and deactivation of selective neuronal population using optogenetics and chemogenetics and all the intersectional strategies far exceeds neuropharmacological approaches, which were previously so important. I saw so many novel agonists and antagonists become available; getting access was key!

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The changes in *in vivo* electrophysiology, including the development of optrodes, which allows simultaneous optogenetics and multi-channel electrophysiological recording, are beyond belief. Of course, many researchers will not know what it was like to make your own electrodes for chronic implantation or, indeed, the equipment to make such recordings. The development of *in vivo* gradient-index (GRIN) lens microendoscopic systems to monitor, in real time, the neurone calcium dynamics (a proxy for neuronal activity) of selective GCaMP-expressing neurones is absolutely amazing, and provides opportunities to monitor neuronal activity at single cell resolution.

'For me, research has never been a job, but a way of life, and I have been paid to do precisely what I want to do, apart from a miniscule amount.'

What have been your career highlights so far?

Working with Ernst Knobil opened my eyes and was so empowering, because it allowed me to compare a genius, a member of the cognitive elite, with others who profess or try to portray those attributes. Finally achieving my goal to engage with computational mathematical modellers was certainly a highlight. The opportunities they provide to expand your mind and research are immeasurable. I have enjoyed working with so many amazing people.

What do you consider your top three publications (Impact Factor/citation index aside)?

It is very hard to select three papers, because I am fond of many for very different reasons. I also have a very bad attitude towards Impact Factors, which might be construed as political naivety, but I don't care!

Publication 1: O'Byrne KT, Thalabard JC, Grosser PM, Wilson RC, Williams CL, Chen MD, Ladendorf D, Hotchkiss J & Knobil E 1991 Radiotelemetric monitoring of hypothalamic GnRH pulse generator activity throughout the menstrual cycle of the rhesus monkey *Endocrinology* **129** 1207–1214.

The opportunity to conduct such research on a higher primate was an amazing privilege. It advanced our understanding of how the GnRH pulse generator operated across the menstrual cycle, especially at the time of the preovulatory LH surge, and challenged established dogma, which was rather amusing.

Publication 2: Comninos AN, Anastasovska J, Sahuri-Arisoylu M, Li X, Li S, Hu M, Jayasena CN, Ghatei MA, Bloom SR, Matthews PM, O'Byrne KT, Bell JD & Dhillo WS 2016 Kisspeptin signaling in the amygdala modulates reproductive hormone secretion *Brain Structure & Function* **221** 2035–2047.

Serendipity played out here. The opportunity to collaborate with Waljit Dhillo and his amazing team at Imperial was and is such a pleasure. A casual conversation led to this study, and opened up a completely new avenue of research. It highlighted the importance of kisspeptin signalling in the amygdala, part of the emotional limbic brain, as an upstream regulator of the GnRH pulse generator, involved in pubertal timing and stress-related infertility. It led to many future studies and funding opportunities.

Publication 3: Voliotis M, Li XF, De Burgh R, Lass G, Lightman SL, O'Byrne KT & Tsaneva-Atanasova K 2019 Mathematical modelling elucidates core mechanisms underpinning GnRH pulse generation *Journal of Neuroscience* **39** 9738–9747.

This was the first paper that came out of the collaboration with my Exeter computation modellers. This was mind-blowing. As experimentalists, we confirmed the modelling prediction that if you increase the basal activity of the arcuate nucleus kisspeptin neuronal network using optogenetics, you can initiate *pulsatile release of LH. Increasing basal activity further increased GnRH pulse generator frequency, and if you continue to increase basal activity you cross an upper bifurcation point and switch off the oscillator. Again, the modelling has opened up so many opportunities to address the mechanism, which would not have been possible otherwise.*

How important have the research environment and endocrine community been in shaping your research?

For me, research has never been a job, but a way of life, and I have been paid to do precisely what I want to do, apart from a miniscule amount. I have had the privilege of being surrounded by remarkable colleagues from the endocrine community, and their contribution to my research is immeasurable. My collaborators have been the cornerstone of my research endeavours.

Finally, what is your advice for endocrine trainees who are forging a career in endocrinology?

Have confidence in yourself; that is the most important thing in life. We are great at placing hurdles in our way, e.g. 'I can't put that technique in my fellowship or grant because I don't have experience or preliminary data'! If the said technique puts you ahead of the game, then put it in. Don't assume that your so-called superiors know what they are talking about. Take advice from as many sources as you can. Learn to say NO. Be highly selective in choosing your collaborators: any doubts, no matter how subtle, walk away. Our subconscious intuition is more powerful than we imagine. Science has got to be fun.

Although the condition might be rare...

...the features are common

Perhaps it's Cushing's syndrome, perhaps it's something else? If you connect any of these dots within a patient, consider referring them to a specialist endocrinologist.

For a clinician's guide to recognising Cushing's syndrome's signs and features, email **cushings@connectthedots.health** and help shine a light on this rare condition.

HRA Pharma Rare Diseases is now part of ESTEVE

Connect the dots

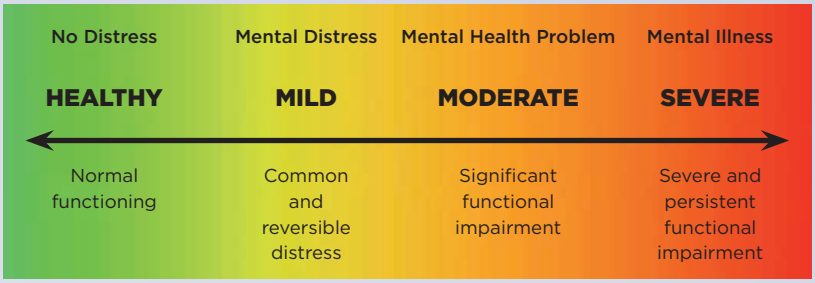
References: 1. Pappachan JM *et al. J Clin Pathol.* 2017;70:350–359. doi:10.1136/jclinpath-2016-203933
2. Nieman LK. *Endocrinol Metab.* 2018;33:139–146. 3. Yorke E *et al. Int J Endocrinol.* 2017; 1547358.

UK/NPR/0031 Date of preparation: August 2024

HOW TO... LOOK AFTER YOUR MENTAL HEALTH

WRITTEN BY ASHLEY CAVE

Maintaining good mental health is essential for our own overall well-being, and also for productivity. Stress, anxiety and other mental health difficulties can significantly impact our professional and personal life.



The mental health continuum.

I like to see mental health as being on a continuum (see Figure). Most of the time we aim to stay in the 'healthy' zone, where we function at home and at work. It's normal for us to fluctuate quite frequently into the mild zone: perhaps we have a lot on at work, or home life is challenging, or we might have experienced a loss of some description. Movement into the 'yellow' zone on the Figure is normal and expected. It's also common and reversible so, even if function is impaired, we have hope and knowledge that we will drift back into the 'green'.

The World Health Organization[1] describes mental health as 'A state of mental well-being that enables people to cope with the stresses of life, realise their abilities, learn well and work well, and contribute to their community.'

Just as we take care of our physical health by taking vitamins, exercising, and getting check-ups with a GP, we also need to prioritise our mental health. There isn't a 'one size fits all' approach to managing mental health, but there are some evidence-based methods we can use from day to day to stay in the 'green.'

PRIORITISE SELF-CARE

This is the foundation for good mental health for anyone, whether you have a diagnosis of a mental health difficulty or not.

- Aim to get a good night's sleep: have a routine (where possible around work, family, etc.) that allows you to wind down a bit each evening. Aim to get 7–9 hours of sleep each night.
- Eat well: having a good, balanced diet is not to be underestimated.
- Move more! Exercise and movement boast incredible benefits for both mental health and physical health. One study has shown that exercise reduces the risk of depression by around 25%.[2]

If you feel you are starting to drift into the yellow zone, it's helpful to take a step back from whatever might be triggering that slight shift in mental health. Look at how you might be managing stress levels. Often, people will turn to something that helps in the short term to get through a stressful event. This can sometimes be a glass of wine (or more!) or withdrawing from others to cope. We know that these are not healthy coping mechanisms, even if they feel good in the short term. There are many other things that can help us manage stress:

- Deep breathing, meditation or mindfulness: all of these methods are accessible via a good quality YouTube channel and can reverse the physical feelings that stress and anxiety bring.
- Taking breaks and implementing time management: set small goals and use lists to help when feeling overwhelmed with work or home life.
- Stay connected: see friends, talk about how you're feeling, plan something nice to do with others socially.
- Set boundaries: clearly define the time that is yours, the time for family and the time for work.

SEEKING HELP

Drifting into the orange or red zone might be an indicator for seeking professional support via NHS talking therapies[3] or a GP. Self-monitoring can help you to identify changes in mood, energy levels and sleep that might indicate that more support is needed. Sometimes this might be in the form of medication, or in other instances talking therapies, or a combination of both.

ASHLEY CAVE
Mental Health Advisor, Student Journey (Sport and Support), University of Sunderland

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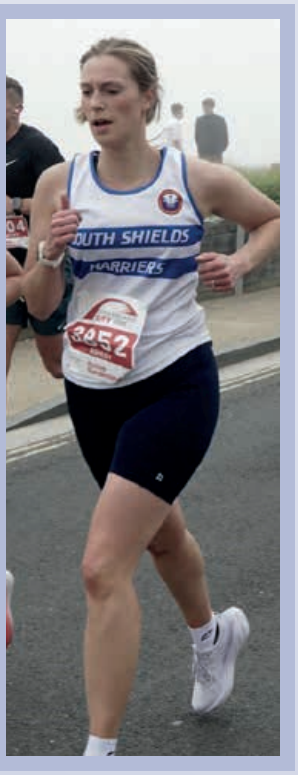
1. World Health Organization 2022 *Mental Health* www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response.
2. Pearce M *et al.* 2022 *JAMA Psychiatry* https://doi.org/10.1001/jamapsychiatry.2022.0609.
3. NHS 2022 *NHS Talking Therapies for Anxiety and Depression* www.nhs.uk/mental-health/talking-therapies-medicine-treatments/talking-therapies-and-counselling/nhs-talking-therapies.

RUNNING: MY PERSONAL APPROACH

Key to success is finding out what works for you in managing your mental health. Personally, I found that starting running after the birth of my first child around 11 years ago has been hugely beneficial to my own mental health. It's now something that has become a regular part of my week.

Tips for getting into running:

- Look up your local **Parkrun:** this is the most inclusive, welcoming running environment. It's a social intervention masked as a running group; there is a role and a place for all.
- Find a podcast or audible book that you love: the drive to hear more can get you out of the door!
- Have support to run: whether it's your partner watching kids for you, an online group spurring you on or a new running buddy. All of these will make it easier to embed movement/running into your weekly schedule.



Society for Endocrinology

SfE BES HARROGATE 2025

SfE BES IS BACK!

After taking a break in 2024, the Society for Endocrinology BES conference will return to Harrogate from 10 to 12 March 2025.

Join the largest gathering of endocrine professionals in the UK, as we learn from each other, share our passion for endocrinology and collectively work towards advancing research and patient care in our field.

SUBMIT YOUR ABSTRACT

Are you ready to share your research at SfE BES 2025? Submitting an abstract to the conference provides a fantastic opportunity to gain insightful feedback from our community to progress your work. It's also a great way to enhance your professional profile and forge new connections with colleagues working in your specialty.

ABSTRACT SUBMISSION DEADLINE

Monday 28 October 2024 (11:59pm GMT)

SAVE ON YOUR REGISTRATION

Early bird deadline: Wednesday 18 December 2024 (11:59pm GMT)

Why you should apply for the LEADERSHIP AND DEVELOPMENT AWARDS PROGRAMME

EMPOWERING THE NEXT GENERATION OF LEADERS IN ENDOCRINOLOGY

Following recommendations from the Society's 2023 Equality, Diversity and Inclusivity Report, we have opened up the Leadership and Development Awards Programme to all members. We believe our members have the potential to become leaders in endocrinology, regardless of their background, member category or specialty. This programme is designed to recognise and nurture emerging talent, equipping you for future leadership roles in our field.

As well as leadership training and support to attend our SfE BES conference, you will receive opportunities to network with senior endocrinologists and get involved with meaningful Society initiatives that will support your career development into the future. Places are limited each year, so if you'd like to be among the first to find out when applications open and receive important updates on the programme, **register your email address.**

HEAR WHY YOU SHOULD GIVE IT A GO FROM OUR AWARDEES THEMSELVES:

YOU SHOULD APPLY!

"The Leadership and Development Awards Programme has been a great way to network and get more involved with Society activities, especially during SfE BES conferences. There have been many chances to contribute, including chairing sessions and judging posters. There is so much to be gained; being part of the programme affords so many different opportunities. Moreover, it's a really enjoyable and worthwhile experience.

DOUGLAS GIBSON

MANY OPPORTUNITIES

"It increases opportunities to understand how various committees work in the Society. Just apply for it. If you don't get it, you will receive feedback to understand what's missing. You can then work on it and then apply again the following year.

PUNITH KEMPEGOWDA

SO MUCH TO GAIN

"[My highlights are] meeting a wide range of people within the Society, all the support we have been given… as well as the variety of opportunities to be involved in Society activities. Apply, and if you do not get an award the first time, please try again, because you have so much to gain.

CHIOMA IZZI-ENGBEAYA

Take the lead!
JOIN ONE OF YOUR SOCIETY'S COMMITTEES

- **Do you want to help shape the future of your Society?**
- **Do you want to use your skills in new ways and expand your professional network?**
- **Then apply for one of our 2025 vacancies**

We need many voices to be represented in the Society's leadership, so we can adapt to support endocrinology into the future. We're on the lookout for members from all career levels, backgrounds, locations and specialties, who can bring fresh perspectives to our Council of Management and Committees, to maximise the impact of the Society.

If you're motivated to make a difference and keen to help shape a positive, successful future for endocrinology, then we'd like you to join us!

WHY SHOULD YOU JOIN THE TEAM?

By joining your Society's leadership team you can make meaningful changes happen within both the Society and the field of endocrinology. You can support the next generation of endocrinologists, enhance patient care, and empower people to make better decisions about their health. You'll also expand your professional network and have the opportunity to use your skills in new ways.

CURRENT VACANCIES

Council of Management
- President-elect
- Council Member

Committee Chairs
- Clinical Committee Chair-elect
- Corporate Liaison Committee Chair-elect
- Nurse Committee Chair-elect

Committee Members
- Clinical Committee *3 vacancies*
- Corporate Liaison Committee *5 vacancies*
- Events and Training Committee *4 vacancies*
- Grants Committee: *1 vacancy*
- Nominations Committee *3 vacancies*
- Nurse Committee: *4 vacancies*
- Programme Committee *4 vacancies*
- Public Engagement Committee *3 vacancies*
- Science Committee *2 vacancies*

There are also opportunities to become an Endocrine Network Convenor, and to sit on the Leadership and Development Awards Selection Panel.

WHAT DO CURRENT COMMITTEE MEMBERS SAY?

"I hadn't realised how welcoming the Committees would be. They are approachable and they value your contribution; everyone's views are respected. If you are interested in a role, apply for it! You will learn something new, the experience will be beneficial to your career and you can help to develop areas within the Society that benefit its members.

JOANNE BROWN, Nurse Committee

"I have met and networked with lots of new people through being on the Public Engagement Committee. I really enjoy attending the meetings, and the social aspect of being involved in the group!

ABIGAIL BYFORD, Public Engagement Committee

"The other people on the Committee are lovely, and it's interesting to hear about their experiences in their institution and at their career stage. As Mahatma Gandhi said, "The best way to find yourself is to lose yourself in the service of others." I would encourage people to apply, and bring fresh perspectives and ideas to the role. What would success look like? Making positive contributions to the community.

CRAIG BEALL, Science Committee

YOUR CHANCE TO APPLY

Find out more about our current vacancies, and how to apply

Joanne Brown on GROWING A NETWORK ON THE NURSE COMMITTEE

Joanne Brown was the first Endocrine Clinical Nurse Specialist at Stockport NHS Foundation Trust. She has had an active part in the Society's Committees since 2021, joining the Nurse Committee in 2022. She tells us about her nursing career path, and how joining our Committee helped her grow both her network and her confidence.

How did you become involved with governance at the Society?
I commenced the Endocrine Clinical Nurse Specialist role at Stockport NHS Foundation Trust in March 2020, during the COVID-19 pandemic. This was a brand new role for the Trust and I initially worked from home, as I had to shield at that time.

My background is in critical care and neurosurgery as an Advanced Nurse Practitioner. As I was new to the Endocrine Specialist Nurse role and was working alone from home, I reached out to the Society for Endocrinology for support. I then became more involved with the Society and was keen to contribute as a voice for Early Career Nurses, so I applied and joined the Early Career Steering Group in March 2021, which later became the Early Career Committee. I then joined the Nurse Committee in January 2022, and am still a part of that today.

How did your experience support your role in governance?
Having previously been an experienced Advanced Nurse Practitioner in both neurosurgery and critical care, I was aware of my knowledge gaps in endocrinology when I moved to the field. I had ideas about the support I needed to bridge these gaps. For example, I had limited knowledge and experience in setting up a nurse-led clinic and needed to develop my skills in managing adrenal adenomas, amongst other things.

Having had experience networking and presenting at a regional conference in my previous roles, I shared my needs with the Society, suggesting that webinars on different subjects might help myself and the wider Early Career Nurse community, and that I was happy to host and present within these webinars. I also felt that networking and supporting each other with guidance from more experienced endocrine nurses would be beneficial for lots of Early Career Nurses. By joining the Early Career Committee, I was able to voice their ideas and my own thoughts. This experience then gave me the confidence to apply for a position on the Nurse Committee.

'If you are interested in a role, apply for the position: you will learn something new, the experience will be beneficial to your career and you can help to develop areas within the Society that benefit its members.'

What did you expect before you took up your role?
I hadn't realised how welcoming the Committees would be. They are approachable and they value your contribution; everyone's views or opinions are respected. I was concerned about the commitment needed to attend meetings, but this is actually very easily managed. Advance notice is given of meetings and, if I am unable to attend a meeting face-to-face, there has always been the opportunity to attend them virtually. Therefore, being involved with the Committee has not impacted my clinical workload.

What have your highlights been?
I have enjoyed gaining experience at both the Endocrine Nurse Updates and the SfE BES conferences, as well as the opportunity to co-Chair presentations. Through these Committee roles, I have had the confidence to make suggestions and help develop a Regional Endocrine Nurse Network for the Northern Region.

My Committee roles have been invaluable for networking with experienced endocrine nurses, who have supported me with my role and development. Having been a lone worker in my role at Stockport NHS Foundation Trust, I can say that the Committees help you to feel part of a wider specialist nurse team.

The Committees also support you to expand your knowledge, which empowered me to develop the service I deliver at Stockport NHS Foundation Trust, and so improve patient care. I have also had the opportunity to contribute to **The Endocrine Post** and to co-write an article for ***The Endocrinologist***.

Has anything surprised you about the role?
I didn't realise how many opportunities there are to input at a national level, both at conferences and on major issues such as NICE guidelines. I found it was interesting to work alongside scientists and researchers within the Early Career Committee, as this was a new experience for me. It is good to learn about other roles within endocrinology.

What is your advice for members who are interested in applying for a Committee role?
Reach out to Committee members and the Society, and talk to them about the roles. If you are interested in a role, apply for the position: you will learn something new, the experience will be beneficial to your career and you can help to develop areas within the Society that benefit its members. Get involved!

DON'T MISS OUT!
Find out more about Committee and Council vacancies and apply

Ali Abbara on
MAKING AN IMPACT WITH THE PUBLIC ENGAGEMENT COMMITTEE

Ali Abbara is Clinical Senior Lecturer in Diabetes and Endocrinology, based in the Department of Metabolism, Digestion and Reproduction at Imperial College London. He has received prestigious fellowships from the National Institute for Health and Care Research (NIHR) and the Wellcome Trust.

Ali has been actively involved with the Society's public engagement, from schools outreach events to being Editor of our public-facing website **You and Your Hormones**. In 2019, Ali joined the Public Engagement Committee. He tells us about his experience of the role, and why you should get involved with Society governance by applying for a Committee position.

How did you become involved with governance at the Society?
As a clinical academic funded by the NIHR, I had long been involved in public engagement activities to communicate research findings to patients and the public in an accessible manner. So, I was keen to contribute to the Society's public engagement activities.

'The schools events have always been great fun, and it's great to enthuse young prospective endocrinologists of the future.'

I applied to join the Public Engagement Committee, which has been a wonderful experience. I also applied to be a content editor for You and Your Hormones, which aims to provide patients and the public with reliable information from our expert members. As a content editor, I reviewed articles to ensure that they remained up-to-date and accurate, and checked that the style and language were suitable for a general audience. Later, I joined the You and Your Hormones Editorial Board and, more recently, became the Editor. As we move forwards, a major focus is to try to increase the audiovisual content offered on the website, in addition to the existing written articles, to engage even more people.

How did your experience support your role in governance?
Although I had some experience with public engagement before joining the Committee, it was not a prerequisite, and many experienced colleagues were able to provide support if needed. So, do apply too, if you are enthusiastic about engaging with the public to promote and help increase understanding of endocrinology.

What did you expect before you took up your role?
I didn't know what to expect from my first Committee role. Generally, there are a couple of meetings per year, and different members of the Committee will take more of a lead on specific public engagement activities, such as running public engagement events, student video awards, evaluating public engagement grants, and engaging with students and teachers from schools to support aspects of the curriculum related to endocrinology (e.g. producing a short video on the menstrual cycle).

What have your highlights been?
The schools events have always been great fun, and it's great to enthuse young prospective endocrinologists of the future. Some of these events coincide with the annual SfE BES conference, where local schools are invited to attend and engage with our members, and take part in some interactive learning activities.

'The Society is always looking for enthusiastic members to join the Committees and contribute to the betterment of our specialty.'

Has anything surprised you about the role?
There were far more ongoing engagement activities than I had realised before I joined the Committee. I am sure this has a huge impact on the public's understanding and enthusiasm for our specialty. It is great to get involved in the Society's Committees, to be more aware of the activities that you can contribute to.

What is your advice for members who are interested in applying for a Committee role?
I would highly recommend applying! The Society is always looking for enthusiastic members to join the Committees and contribute to the betterment of our specialty. You will find being on a Committee very enjoyable. It enables you to meet and share ideas with other like-minded Society members, and it can open up further opportunities to get involved and support the Society's activities in ways you might not have envisioned.

DON'T MISS OUT!
Find out more about Committee and Council vacancies and apply

It's now easy to support the next generation of endocrinologists **WITH A DONATION TO YOUR SOCIETY**

The Society exists to support the endocrine community and to help ensure the strength of our specialty for the years ahead.

We have recently launched a **new fundraising section of our website**, where there are a number of ways you can support the next generation. With options from donations and legacies to easyfundraising and exclusive Society merchandise, it's never been easier to support our important work.

HOW WILL YOUR GIFT SUPPORT US?

Every penny that the Society raises will be used to support the endocrine community. Your donation will support our work to:

- invest in the future of endocrinologists, through training events and as grants that provide career-changing funding
- improve the equitable delivery of excellent patient care through our real-world data registries, interdepartmental peer review scheme, and Clinical Resource Hub
- advance endocrine science through the publication and promotion of cutting-edge endocrine research at our events and in our Society journals
- tackle health misinformation and provide accurate resources on hormone health through our public-facing website, You and Your Hormones
- raise the profile of endocrinology as an attractive career choice for scientists, clinicians, nurses and associated professionals, strengthening our discipline into the future.

If you want to make a gift to support a particular area of work, or would like information on leaving a gift in your will, just contact **fundraising@endocrinology.org**.

HOW CAN YOU DONATE?

- You can **make a one-off donation** through our secure online payment system of an amount of your choice, and UK taxpayers can select Gift Aid, to increase donations by 25% at no extra cost.
- Register with **easyfundraising** to donate to the Society when you shop! easyfundraising partners with over 7,000 brands (including the Trainline, Booking.com, ASOS and John Lewis) to donate a portion of the sale to us at no extra cost to you: **find out more, and get started today**.

easyfundraising

- Explore our **Society branded merchandise store**: from T-shirts to water bottles, a portion of the proceeds from sales of all online items are received as a donation. Why not treat yourself, or the endocrinologist in your life?

Supporting you and your patients
USING PATIENT SUPPORT GROUPS

WRITTEN BY PHILIPPA SHARMAN

Often borne out of necessity, and built with resilience and passion, patient support groups (PSGs) can become a lifeline for many, providing support, accurate information and practical tips.

Patient support groups at SfE BES 2023.

When diagnosed with an endocrine condition, patients can face a burden, often described as 'the full-time job I never asked for'. Managing a chronic condition requires assistance and, when your condition is rare and life-threatening, this comes with further complications. Healthcare professionals can only do so much when clinic time and resource are limited, even more so given the current challenges facing the NHS. This is where PSGs come in.

PSGs are there after diagnosis, and for the ongoing education and training required to manage a lifelong condition. Patients and their families can come to us for peer support and expert guidance, avoiding the pitfalls of inaccurate information on the internet and social media. We bridge the gap between appointments to engage, educate and empower patients and those who support them.

Whilst we cannot wave a magic wand to remove waiting times and delays, there is a lot we can do to support and educate the community whilst they wait. We can also try and remove some of the pressures from you and your endocrinology departments.

OPPORTUNITIES FOR HEALTHCARE PROFESSIONALS

We do not exist for the benefit of patients alone. We provide up-to-date, reliable, expert-reviewed information and research opportunities for healthcare professionals. By getting involved with PSGs, you can gain a more well-rounded understanding of a condition's diagnosis, progression and impact on patients' lives.

Many PSGs are also able to provide research grants and, with most research funders wanting to see engagement and involvement with the public, PSGs can provide vital links to help demonstrate the impact of your work.

PSGs also want to hear from you, to develop our shared understanding of what everyone needs to manage conditions effectively and to improve patient safety and quality of life. Have you noticed an education gap within a condition you treat? Let us know!

PSGs are vitally supported by healthcare professionals like you, volunteering as medical advisors, sitting on clinical advisory panels and standing as medical trustees. We are truly grateful for all you give to support our work and make our expert guidance available.

WORKING TOGETHER, WE ARE STRONGER

Ultimately, collaborations between PSGs and healthcare professionals contribute to the well-being of all involved! Living with chronic conditions requires constant self-management, access to high quality information and social support – all of which can be provided by PSGs. When combined with a healthcare professional who is well-informed, actively involved in the management of a rare condition and collaborating with the relevant PSG, the patients' care and lived experience can be significantly enhanced.

EXAMPLES OF PSGs' RECENT WORK

- Speaking at the Getting It Right First Time 'Further Faster' Endocrinology meeting in June 2024, the **Addison's Disease Self-Help Group**, **British Thyroid Foundation** and **The Pituitary Foundation** highlighted their resources for patients and clinicians and suggested how QR codes on appointment and clinic letters linking to PSGs would support patients through extended waiting times. These presentations will be available to watch on **NHSFutures**.
- The **Child Growth Foundation** has developed a range of transition resources for young people affected by growth conditions, beginning with Silver–Russell Syndrome. Additionally, with their medical advisors, they have launched GP virtual training sessions on the education platform Pulse 365, which will be rolled out to a larger audience of healthcare professionals.
- The **Association for Multiple Endocrine Neoplasia Disorders** raised awareness of patient needs, presenting at conferences including the World MEN Scientific Meeting and the SfE BES conference in 2023, and the South Korean SICEM conference in 2024.
- The **Brittle Bone Society** is proud to act as Secretariat of the NHS Rare Disease Collaborative Network (RDCN) for Adult Rare Bone Disease. The aim of the RDCN is to establish a robust network which, at this time, involves 18 hospital trusts in England.
- The **British Thyroid Association** worked with MIMS Learning to produce free continuing professional development webinars and training modules for healthcare professionals which are endorsed by the Society for Endocrinology.
- **PWSA UK** (for Prader–Willi syndrome) awareness month culminated in Glow Orange on 31 May, and this year saw 39 national landmarks (including Battersea Power Station) lit up orange!

ABOUT THE SOCIETY'S PSG NETWORK

In September 2021, the **Society for Endocrinology PSG network** was established, with representation from 18 Society-affiliated PSGs and representatives from the Nurse and Clinical Committees. The network provides a forum to share concerns and best practice in a collaborative and supportive environment. Meetings are held twice per year, with the agenda driven by the PSGs.

The network has helped to streamline the PSG affiliation process, enabled improved engagement with PSGs at Society events, facilitated the development of new tools for patient engagement and provided a stronger voice for PSGs within the Society. The network also provides invaluable input to key Society projects, with important contributions to the Defining the Future of Endocrinology working group, highlighting the importance of a closer working relationship with the Society.

PHILIPPA SHARMAN
Communications and Research Manager,
Addison's Disease Self-Help Group

FURTHER READING

Breen L *et al.* 2023 *Endocrine Abstracts* https://doi.org/10.1530/endoabs.94.P154.

Society for Endocrinology

IRISH ENDOCRINE SOCIETY

Joint Irish–UK Endocrine Meeting 2024

14–15 October 2024
ICC, Belfast

JOIN THE EXCITEMENT IN BELFAST!

We look forward to seeing you there

The Society for Endocrinology and the Irish Endocrine Society are excited to host the Joint Irish–UK Endocrine Meeting. This special collaboration aims to advance the field of endocrinology across the UK and Ireland.

There's still time to register. Don't miss out – secure your spot today!

An interview with…
LI CHAN
PAEDIATRIC ENDOCRINOLOGY AND LIFELONG HEALTH

Li Chan is Professor of Molecular Endocrinology and Metabolism and Honorary Consultant in Paediatric Endocrinology at Queen Mary University of London (QMUL) and Barts Health. She has co-led the **Lifelong Health (LLH)** multidisciplinary theme at QMUL and UKRI ageing network CELLO. Here, Zin Htut, Editorial Board member of *The Endocrinologist*, took an opportunity to ask Professor Chan about her career to date.

Please tell us about your background, and what drew you to paediatric endocrinology

My endocrinology journey started as a medical student in Cambridge. I distinctly remember a biochemistry book with a figure of Cushing's disease that sparked my interest in hormones. Through serendipity, I was then a house officer on the endocrinology ward working with Steve O'Rahilly, Krish Chatterjee and Sadaf Farooqi. Not realising at the time, those 6 months laid the foundations for an endocrine career. Later, as a senior house officer in paediatrics, I met Martin Savage, who drew me into paediatric endocrinology through seeing and diagnosing complex cases and co-authoring papers. Les Perry (biochemist) sat in clinic with us, discussing hormones, normal values and assays, which was fascinating, and I was hooked. Martin introduced me to Adrian Clark, and during that time, I applied for funding, got funding, and did a PhD. The rest is history.

What has been your biggest challenge?

So, I think there are challenges throughout a career, both at home and work. Getting a PhD was a massive challenge, because funding is hard to achieve. Early on, I was relatively successful in securing grants. But, once you become a principal investigator, it is completely different. Grant success rates are low – around one in five or one in eight – meaning you face months of effort and the depression of rejection. Yet, you need that drive to find answers to scientific questions and keep your lab running. Another major challenge is work–life balance, especially starting a family. Children can delay career progress, creating publication and grant gaps, which I often discuss with other female academics.

How do you balance your roles as doctor, researcher and mother?

It's about finding what works for you. When I had kids, we shared parental leave and I went part-time which worked for us. Many parents inevitably feel guilty on all fronts: home, academic and clinical. Give yourself a break as there is a limit to what you can do, but at the same time, try not to lose track of why you're doing this job. Asking scientific questions and finding answers in academic medicine drives me to carry on.

What have been your goals within the Lifelong Health initiative?

This was a new strategic theme in QMUL, to think about an unmet need. The population is ageing and people are living longer, but they are not necessarily healthier. From my perspective as a paediatrician working on metabolism, understanding the early years and their impact on later health is crucial. I have been working with Siân Henson, an old-age biologist, on this Lifelong Health theme. We realised we could co-lead this role, since I cover clinical paediatrics and she covers ageing basic science. As leads for the Lifelong Health theme (as well as leads for a UKRI ageing network called CELLO) we focus on a life course approach to healthy ageing from early years to older ages, particularly in the areas of metabolism and rare diseases.

We have recruited three senior lecturers to push this agenda within QMUL and created an interdisciplinary network where biologists, social scientists and data scientists can collaborate. Our main goal has been to get people talking and working together on big questions about improving healthy life course. This requires more than just biologists: it needs policymakers and the community.

We also established educational and public engagement aspects, to train the next generation of researchers from grassroots onwards and connect with the community. Breaking down silos and developing interdisciplinarity was a key vision of ours as part of both LLH and CELLO. It has been a challenge but I think we've made good progress.

Sharing leadership roles has been a revelation, making the journey more enjoyable and productive. I would highly recommend it! Co-leading with Siân has been great. We have pushed each other in directions we would not have undertaken otherwise, truly becoming more than the sum of our parts.

What exciting projects are coming up in Lifelong Health?

There's a lot happening. We've recruited some great people and secured funding. We have someone who's focusing on glucose regulation in the hypothalamus, which is really exciting. Another researcher is looking into ageing and cardiovascular disease. Overall, I believe the key to our future in the theme lies in these new recruits: they will driving success in the years to come.

What advice would you give to someone interested in paediatric endocrinology?

Expose yourself to as many patients, conferences and discussions as you can. I see endocrinology as a spectrum, and I have learned a lot from my colleagues in adult endocrinology. During my training, attending adult endocrine meetings was very educational. For anyone interested in endocrinology, grasp the basics, engage in discussions and seize opportunities. Whether you're interested in academic or clinical work, talk to people and establish independent mentors in and outside your field.

Congratulations on your 2024 *European Journal of Endocrinology* Award. Is there anything you'd like to share?

It was a privilege to be nominated and receiving the award. I thank everyone who has supported me through my journey to date. I hope to continue to answer scientific questions and contribute to knowledge. Clinical academics face many changes; it's tough to balance clinical duties with academic research. As a clinician who runs a basic science, translational lab I am concerned that the traditional 'clinician scientist' career path is becoming more difficult and less attractive. Increasingly there is a view the clinicians should stick with clinical research or trials, which is short sighted and perpetuates the narrative that clinicians cannot do basic science. There are many clinician scientists in endocrinology that demonstrate this is not the case. I hope funders realise this, and continue to support the development of trainees/clinical academics undertaking basic, pre-clinical research.

JOHN HONOUR
MY CAREER IN ENDOCRINOLOGY

John Honour is an Honorary Senior Research Associate at the Institute for Women's Health at University College London, and was previously a Consultant Clinical Scientist in Clinical Biochemistry at UCLH and Head of the Specialist Service for Steroid Endocrinology. His long career has focused on steroid analysis in the context of understanding disease, with an interest in the impact of bacteria on steroid metabolism.

MY EARLY CAREER

I came to a career in endocrinology in 1972, when I joined Cedric Shackleton at the MRC Clinical Research Centre (CRC) in Harrow. Cedric had just started to use capillary column gas chromatography to examine steroids in the urine of patients with adrenal disorders. The stationary phase was a wall coating of silicone polymer on the glass column; this was held in place with heat-shrink polytetrafluoroethylene. The capillary column was 30m long and 0.1cm wide, and replaced the original glass columns (these were often 4m long and 0.5cm in diameter, filled with diatomaceous earth coated with stationary phase). Glass capillaries were replaced with fused silica which was more robust. In 1978, the CRC team produced an atlas of the steroid profiles seen to that time. I suppose we can say this was near the start of metabolomics.

The Clinical Chemistry Department was equipped with a magnetic sector mass spectrometer that almost filled the room, and was probably 20 times bigger than current gas chromatography–mass spectrometry (GC–MS) systems. One important study for me was to perform urinary steroid profile analysis on samples from a patient whom we found to have a rare form of congenital adrenal hyperplasia from 17-hydroxylase deficiency. The steroids we found were metabolites of corticosterone and progesterone, but as well as hepatic metabolites there were products of an enterohepatic circulation with bacterial transformation, notably 21-dehydroxylation. Although this was many years before the universal use of the microbiome that we see today, the bacterial process had been described by Jan Sjövall and Håkan Eriksson in rats in 1965–1972. Some of this information was useful in interpretation of the patient data.

CLINICAL RESEARCH AND PRACTICE

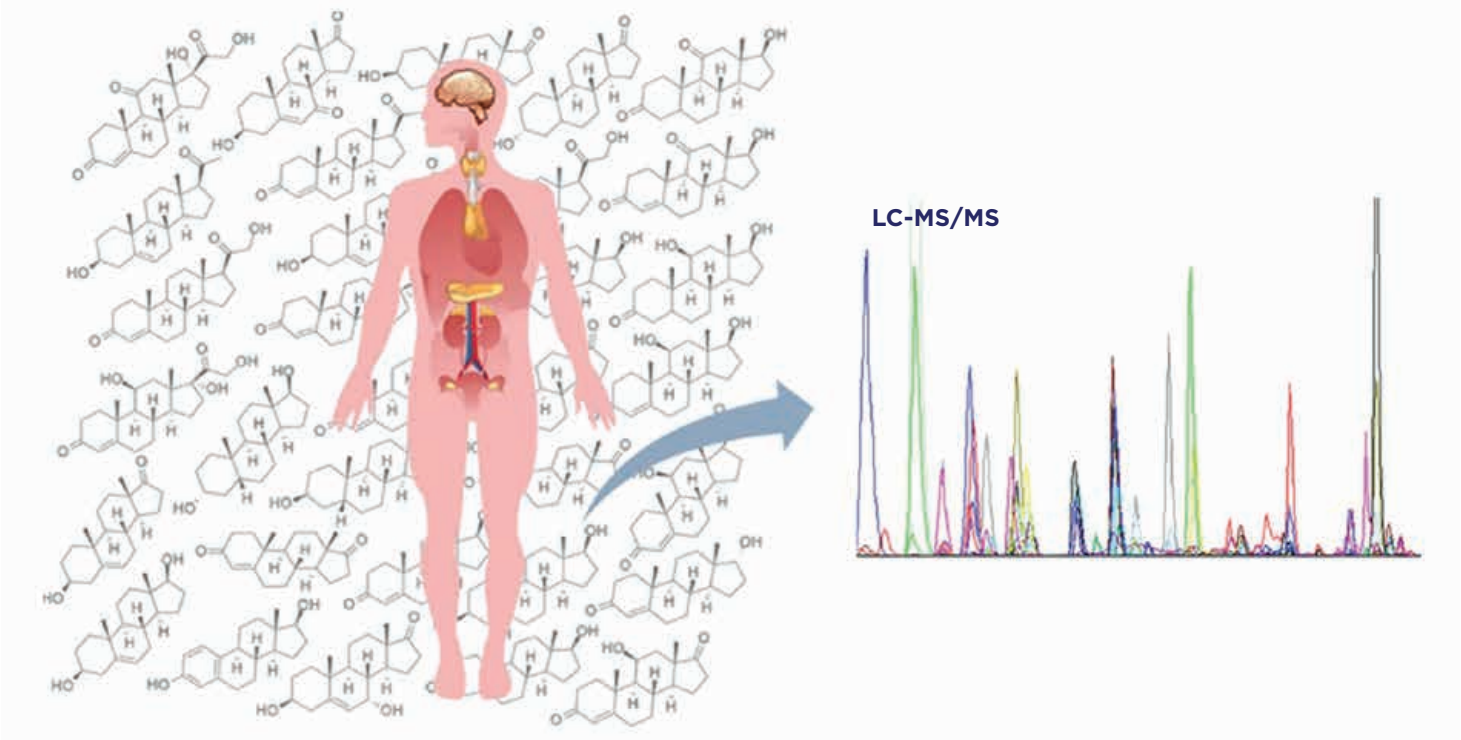
Over the next 40 years at the CRC, Middlesex Hospital and University College London Hospital, I used GC–MS in clinical research. From clinical collaboration, I learnt the need to explain steroid results to clinicians and to act promptly for sick patients. On ward rounds, I saw sick children with adrenal disease and encountered the parents of children who could not be sure of the sex of their baby.

> *'Steroid hormones and their metabolites, once considered inert, are now all known to play important pivotal functional roles.'*

Some clinicians could not see the steroid path beyond the 'chicken wire' (see Figure 1), so there was a need to explain the process of steroidogenesis and metabolism.

Over the years in clinical practice, I encountered patients with almost every known disorder of the adrenal cortex and differences in sexual

Figure 1. Seeing through the 'chicken wire'.



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development. I was involved in clinical research around assisted fertility, polycystic ovary syndrome, preterm infants, osteoporosis, adrenarche, vegetarian diets, hypertension, asthma, AIDS/HIV and septic shock.

For several years, I acted as an expert witness in cases of drug abuse in sport, many due to nandrolone that was found to be in nutritional supplements. The defence of Diane Modahl was based on the demonstration of testosterone formation by bacteria, which acted on steroids in the urine when the sample was left outside the closed laboratory in Lisbon in Portugal, over a weekend in mid-summer. Samples don't get treated like that in the clinical setting.

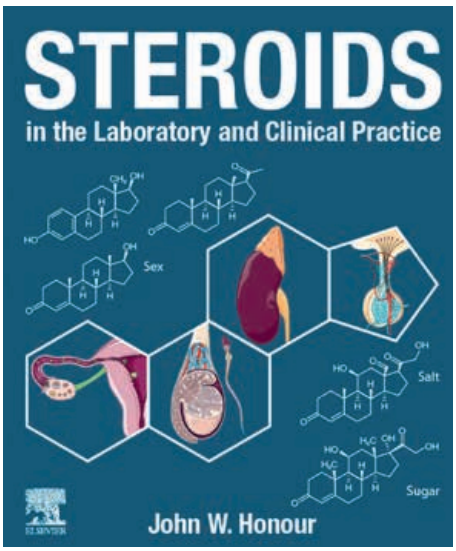
Figure 2. Launching my book among friends.

ADVANCES IN TECHNOLOGY

Towards the end of my career, immunoassay was being discredited thorough lack of specificity and liquid chromatography coupled with mass spectrometry (LC–MS) was becoming popular for steroid analysis. One important attraction was that the steroids did not need to be chemically stabilised for high temperature GC analysis, making the technique more suitable for clinical laboratories. Even steroid conjugates could be analysed directly.

The specificity of LC–MS was improved further by using tandem mass spectrometry (LC–MS/MS), which reflects two mass spectrometers but has three components. After ionisation of the steroid, a fragment ion in the first segment of the mass spectrometer is selected for collision-induced dissociation in stage two, and ions that are then produced are selected for detection in the third stage. Stable isotope-labelled internal standards are ideal. Steroid isomers need to be separated in the LC stage, and it is crucial to test for ion suppression or enhancement by compounds co-eluted into the MS.

Figure 3. My lockdown project, to answer questions around steroids in the laboratory and clinic.



A LOCKDOWN PROJECT

In 2021/2022, after treatment for malignant melanoma, I was in the Government-advised shielding group due to the COVID-19 pandemic. I made use of the time at home to write up my work experience.

In September 2023, this was published as *Steroids in the Laboratory and Clinical Practice*[1] (Figures 2 and 3). No such book had been published in this detail since *Steroid Hormones*[2] by David Gower in 1979, but much had changed since then. The book ended up as a 988-page monster, covering basic chemistry, methods for steroid analysis, and clinical application of steroids. There are more than 730 figures and 120 tables to enhance comprehension of the wide-ranging and often complex material. I hope this labour of love will become the 'go to' for answers to questions around steroids in the laboratory and clinic for pathologists, laboratorians, endocrinologists, analytical/clinical chemists and biochemists.

Steroid hormones and their metabolites, once considered inert, are now all known to play important pivotal functional roles. My professional journey provided me with unmatched broad experiences of steroids in clinical practice that enabled me to write the book for others to benefit.

THE IMPORTANCE OF COLLABORATION

I should acknowledge the many staff in my laboratory and the clinicians locally and around the world with whom I had the privilege to collaborate scientifically, for the benefit of many patients. I must emphasise the need for a dialogue between the parties, because aspects of the investigations are becoming more complicated in different ways for each, so both will benefit from the exchange of information and knowledge.

It's been a pleasure to walk a memory lane of my career and membership of the Society for Endocrinology since around 1975, and the many fruitful meetings with colleagues for exchange of ideas, banter and a few beers.

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1. Honour JW 2023 *Steroids in the Laboratory and Clinical Practice*, 988 pp. Elsevier.
2. Gower DB 1979 *Steroid Hormones*, 116 pp. Yearbook.

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Increase to a maximum of 60 mg for patients whose growth hormone (GH) and/or insulin-like growth factor-1 (IGF-1) levels are not fully controlled after 3 months of treatment with Signifor at 40 mg. *Cushing's disease (adults including elderly and those with renal impairment):* The recommended initial dose is 10 mg by deep intramuscular injection every 4 weeks. Dose may be titrated every 2 to 4 months based on response and tolerability. The maximum dose of Signifor in Cushing's disease is 40 mg every 4 weeks. *Patients with hepatic impairment*: Dose adjustment is not required in patients with mildly impaired hepatic function (Child Pugh A). Not for use in severe hepatic impairment. *Acromegaly:* the recommended dose with moderate hepatic impairment (Child Pugh B) is 20 mg every 4 weeks, and the maximum is 40 mg every 4 weeks. *Cushing's disease:* the recommended initial dose for Cushing's disease patients with moderate hepatic impairment (Child Pugh B) is 10 mg every 4 weeks, and the maximum recommended dose for these patients is 20 mg every 4 weeks. *Method of administration:* Signifor is to be administered by deep intramuscular injection, alternated between left and right gluteal muscle, by a trained healthcare professional. Signifor suspension must only be prepared immediately before administration. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Severe hepatic impairment (Child Pugh C). **Special warnings and precautions for use:** Hyperglycaemia and, less frequently, hypoglycaemia, were observed in subjects participating in clinical studies with pasireotide. Glycaemic status (fasting plasma glucose/haemoglobin A_{1c} [FPG/HbA_{1c}]) should be assessed prior to starting treatment with pasireotide. FPG/HbA_{1c} monitoring during treatment should follow established guidelines. Self monitoring of blood glucose and/or FPG assessments should be done weekly for the first three months and periodically thereafter, as clinically appropriate, as well as over the first four to six weeks after any dose increase. Monitoring of FPG at 4 weeks and HbA_{1c} 3 months after the end of the treatment should be performed. In patients with poor glycaemic control (HbA_{1c} values > 8%), diabetes management and monitoring should be intensified prior to initiation and during pasireotide therapy. Monitoring of liver function is recommended prior to treatment with pasireotide intramuscular use and after the first two to three weeks, then monthly for three months on treatment. Thereafter liver function should be monitored as clinically indicated. Bradycardia has been reported with the use of pasireotide. Careful monitoring is recommended in patients with cardiac disease and/or risk factors for bradycardia. Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or medicinal products to control electrolyte balance, may be necessary. Pasireotide should be used with caution and risk benefit carefully assessed in patients who are at significant risk of developing prolongation of QT. A baseline ECG is recommended prior to initiating therapy with Signifor. Monitoring for an effect on the QTc interval is advisable 21 days after the beginning of the treatment and as clinically indicated thereafter. Hypokalaemia and/or hypomagnesaemia must be corrected prior to administration of Signifor and should be monitored periodically during therapy. The suppression of ACTH secretion can result in hypocortisolism in patients treated with Signifor. It is therefore necessary to monitor and instruct patients on the signs and symptoms associated with hypocortisolism. Ultrasonic examination of the gallbladder before and at 6 to 12 month intervals during Signifor therapy is recommended. The presence of gallstones in Signifor-treated patients is largely asymptomatic; symptomatic stones should be managed according to clinical practice. As the pharmacological activity of pasireotide mimics that of somatostatin, inhibition of pituitary hormones other than GH and/or IGF-1 in patients with acromegaly and ACTH/cortisol in patients with Cushing's disease cannot be ruled out. Monitoring of pituitary function (e.g. TSH/free T_4) before and periodically during Signifor therapy should therefore be considered, as clinically appropriate. If concomitant use of coumarin-derivative or heparin-derivative anticoagulants with Signifor intramuscular use cannot be avoided, patients should be monitored regularly for alterations in their coagulation parameters (PT and PTT) and the anticoagulant dose adjusted accordingly. Signifor should be used with caution in patients with severe renal impairment or end stage renal disease. **Interactions:** Concomitant administration of pasireotide and ciclosporin may require adjustment of the ciclosporin dose to maintain therapeutic levels. Pasireotide should be used with caution in patients receiving medicinal products that prolong the QT interval. Caution also with bradycardic, insulin and antidiabetic medicinal products. **Pregnancy and lactation:** Pasireotide is not recommended for use during pregnancy and in women of childbearing potential who are not using contraception. Breast-feeding should be discontinued during treatment with Signifor. **Effects on ability to drive and use machines:** Patients should be advised to be cautious if they experience fatigue, dizziness or headache during treatment with Signifor. **Side effects:** Effects seen are largely similar between the acromegaly and Cushing's disease indications, and consistent with the class, except for higher degree and frequency of hyperglycamia. *Very common* (≥ 1/10); Hyperglycaemia, diabetes mellitus, diarrhoea, nausea, abdominal pain, cholelithiasis and fatigue. *Common* (≥ 1/100 to < 1/10); Anaemia, adrenal insufficiency, type 2 diabetes mellitus, impaired glucose tolerance, decreased appetite, headache, dizziness, sinus bradycardia, QT prolongation, abdominal distension, vomiting, cholecystitis, cholestasis, alopecia, pruritus, injection site reaction, glycosylated haemoglobin increased, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood glucose increased, blood creatine phosphokinase increased and lipase increased. Other adverse events can include asymptomatic elevations in lipase and amylase and pancreatitis. **Please consult the full SmPC for further information**. **Marketing Authorisation Numbers:** EU/1/12/753/013-019. PLGB 15266/0035-0039. **Legal Classification**: POM. **Price:** One vial of Signifor 10 mg, 20 mg, 30 mg, 40 mg or 60 mg £2,300.00. **Name and Address of the Business Responsible for Sale**: Recordati Rare Diseases UK Ltd., Breakspear Park, Breakspear Way, Hemel Hempstead, HP2 4TZ. Further information is available on request. **Date Prescribing Information Revised**: January 2023.

Adverse events should be reported.
Reporting forms and information can be found at (UK) https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in Google Play or Apple App Store.
(Ireland) Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance www.hpra.ie. Adverse events should also be reported to Recordati Rare Diseases at Tel: +44 (0) 1491 414 333 or RRDpharmacovigilance@recordati.com.