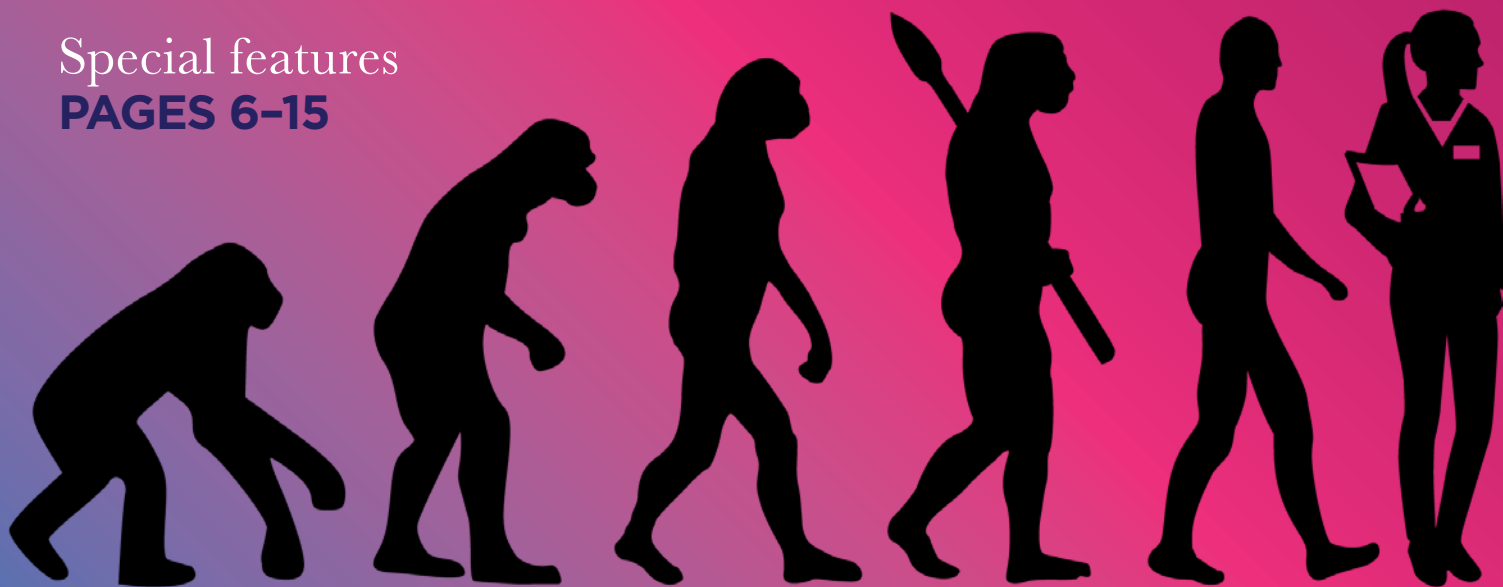


THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

The Next Generation Shaping your future, shaping endocrinology

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A word from THE EDITOR...



Worn down by the burden of winter pressures on the NHS or the demands of grant applications to submit and papers to write, we might not have had time to think about the next generation of endocrinologists, or to consider how we might plant, in them, the same love for endocrinology that we ourselves enjoy. However, as spring approaches, with its promise of rebirth and regeneration, there is an opportunity for us to reflect on how our interest in endocrinology was born and nurtured.

In issue 122 of *The Endocrinologist*, I interviewed our President, Graham Williams, who spoke of those who lit his interest in endocrinology and ignited his passion for research. Many of us can also remember mentors, who found the time to listen, support and encourage us to be the best versions of our endocrine selves. Some of us will also be lucky enough to recollect an inspiring role model who we wanted (or still wish) to be!

This issue of *The Endocrinologist* invites us to consider how we can all engage in sparking the interest of bright young minds in the challenging, diverse, mysterious, fascinating world of endocrinology. Isaac Newton said, 'If I have seen further, it is by standing on the shoulders of giants.' So, with strong shoulders at the ready, let's commit to supporting our up-and-coming colleagues, by encouraging them to see beyond what we ourselves have achieved. In this way, we will shore up the future of endocrinology by growing the very best clinical and scientific talent, generation after generation.

With warmest good wishes

AMIR SAM

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www.endocrinology.org/endocrinologist

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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 Summer 2018 issue: **23 March 2018**.

Front cover image ©Shutterstock



NEW FACES AT THE ENDOCRINOLOGIST

We are delighted to welcome two new members to the Editorial Board of *The Endocrinologist*: Douglas Gibson (Edinburgh) and Louise Hunter (Manchester).

The Editorial Board aims to ensure that the views and interests of all Society members are represented in the magazine. If you would like to contact them with your ideas for articles or feedback, please email endocrinology@endocrinology.org.



Douglas Gibson



Louise Hunter

HAVE YOUR SAY: COUNCIL NOMINATIONS NEEDED

Could you or a colleague be the Society's next Council members? Four positions will be available from November 2018, so get more involved in running your Society and nominate yourself or your choices before **29 June 2018**.

Find out more about the work of Council and download a nomination form at www.endocrinology.org/about-us/governance/society-for-endocrinology-council.

MEET THE 2018 CET VISITING PROFESSOR

Would you like to host a visit from the Clinical Endocrinology Trust Visiting Professor, Chris Thompson? Chris is Consultant Endocrinologist at Beaumont Hospital, Dublin, Ireland. He will be touring the UK in the week before the Society for Endocrinology BES conference, which takes place on 19–21 November 2018. If you would like to host Chris at your institution, please contact members@endocrinology.org.

NOMINATIONS FOR NEXT SOCIETY PRESIDENT

Graham Williams will retire as the Society's President at the 2019 AGM, so nominees are sought to take up the role of President-elect from November 2018.

Council's nominee for this post is Raj Thakker (Oxford).

If any member would like to suggest an alternative, please email the Society office via members@endocrinology.org before **23 March 2018**.

EARLY CAREER PRIZE LECTURES

Read articles from the 2017 Early Career Prize Lecture winners on pp. 12–14. Applications for the 2018 awards are required by **30 April 2018**.

Successful applicants will present a lecture at the Society for Endocrinology BES conference in November 2018 and be awarded an honorarium of £750, in addition to publishing an article in *The Endocrinologist*.

See www.endocrinology.org/grants-and-awards/prizes-and-awards/early-career-prize-lectures for details.

HONE YOUR PUBLIC ENGAGEMENT SKILLS – FREE WORKSHOP

Learn how to communicate your science more effectively at this workshop in Birmingham, 17 April 2018. Register online at www.endocrinology.org/events/public-engagement-training-workshop.



DON'T MISS THESE Sfe BES VIDEO HIGHLIGHTS

A selection of plenary lectures and symposia from Sfe BES 2017 are available to watch online now at www.endocrinology.org/careers/training-and-resources/videos/videos-from-sfe-bes-2017.



REDUCED REGISTRATION FOR EUROPEAN THYROID ASSOCIATION MEETING

Society members are eligible for reduced registration fees to attend the Annual European Thyroid Association Meeting in Newcastle, 15–18 September 2018.

Visit www.eta2018.org for more information, and to register. Please use booking code B2018ETA.



SOCIETY CALENDAR

- 12 March 2018
Sfe NATIONAL CLINICAL CASES MEETING
London
- 16–18 April 2018
CLINICAL UPDATE
Birmingham
- 16–17 April 2018
ENDOCRINE NURSE UPDATE
Birmingham
- 16–18 April 2018
CAREER DEVELOPMENT WORKSHOP
Birmingham
- 17 April 2018
PUBLIC ENGAGEMENT TRAINING WORKSHOP
Birmingham
- 24 September 2018
PITUITARY MASTERCLASS 2018
London
- 19–21 November 2018
Sfe BES 2018
Glasgow

www.endocrinology.org/events for full details



GRANT AND PRIZE DEADLINES

- 14 March 2018
SUMMER STUDENTSHIPS
- 14 March 2018
TRAVEL GRANTS
- 28 March 2018
PUBLIC ENGAGEMENT GRANTS
- 11 April 2018
REGIONAL CLINICAL CASES MEETING GRANTS
- 25 April 2018
PRACTICAL SKILLS GRANTS
- 30 April 2018
EARLY CAREER PRIZE LECTURES

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

WITH REGRET

We are sorry to announce the death of Senior Member, Professor M Dodd (Warwick). A full obituary will appear in the next issue of *The Endocrinologist*.

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

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



JOURNAL OF ENDOCRINOLOGY

Timed feeding and hormone administration for circadian disruption

Shift work, social jet lag and 24/7 lifestyles are thought to add to the burden of metabolic disease facing modern society. Erratic sleep–wake patterns, changing meal times and artificial light exposure lead to dysynchrony of our internal body clocks, potentially increasing the risk of obesity, hyperglycaemia and dyslipidaemia.

Báez-Ruiz and colleagues, from the group of Ruud Buijs, induced circadian disruption in rats by housing them in constant light, rather than a standard cycle of 12h light–12h darkness. This disrupted their rhythms of activity

and of circulating corticosterone, and resulted in triglyceride accumulation, hyperinsulinaemia and impaired glucose tolerance.

Restricting the rats' feeding periods to 12-h windows ameliorated glucose handling, but did not improve other metabolic parameters affected by constant light. However, restoring hormonal rhythms with timed administration of melatonin and corticosterone (secreted in a piece of apple), in phase with feeding, did restore liver triglyceride, bile acids and glucose handling to levels comparable with those in animals housed in a light–darkness cycle. It remains to be seen whether such strategies might translate to humans working nightshifts.

Read the full article in *Journal of Endocrinology* **235** 167–178

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Glucose uptake and signalling in adipocytes with high-fat feeding

Obesity is a major risk factor for the development of type 2 diabetes through the induction of insulin resistance. To understand the mechanisms driving obesity-associated insulin resistance, it is pertinent to characterise the cellular events preceding insulin resistance in adipocytes.

Hansson and colleagues describe the early changes associated with expansion of adipose cell volume and number following 14 days of high-fat feeding in mice. Their findings point towards autophagy as one of the earliest cellular processes that is perturbed in response to short term high-fat feeding. There was

also progressive deterioration of insulin signalling, but interestingly this did not impact glucose uptake.

With respect to the longer term outcomes of their findings, the authors proposed two alternatives: either cellular insulin resistance will develop given enough time, or the observed increase in autophagic activity serves a compensatory protective function to maintain adipocyte function, thus preserving systemic glucose homeostasis. Longer term follow up studies will be key in answering these important questions.

Read the full article in *Journal of Molecular Endocrinology* doi:10.1530/JME-17-0195

ENDOCRINE-RELATED CANCER

Mechanisms driving adrenocortical carcinoma metastasis

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy, with a poor prognosis and no significant new treatment options on the horizon. The best option for cure is surgery. Treatments for metastatic disease rely on the adrenolytic agent mitotane and combination chemotherapy, which are rarely successful.

Lalli & Luconi have reviewed state of the art knowledge of the molecular, immunohistochemical and genomic characterisation of ACC. They describe new immunohistochemistry markers such as the Ki67 labelling index, Wnt, GLUT1 and SF-1. New molecular markers include finding loss of heterozygosity of the imprinted 11p15 region with a deletion of the maternal allele and a

consequent overexpression of *IGF2*, which may be related to overall survival.

They also describe the concept of a 'liquid biopsy': detecting circulating markers of malignancy such as circulating tumour cells, miRNAs, exosomes and circulating cell-free DNA of tumour origin which may provide an early sign of disease recurrence or metastases. Excitingly, a recent mouse model of ACC may provide a means of studying new therapeutic options.

This detailed characterisation of ACC, together with new animal models, will hopefully provide a platform for greater understanding of ACC biology, and development of more successful treatment options to give hope to our patients.

Read the full article in *Endocrine-Related Cancer* **25** R31–R48

ENDOCRINE HIGHLIGHTS

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



Success of female grant applicants: science versus scientist

This year marks a century since some women were given the vote in the UK. Currently, 40% of European science and engineering doctorates are awarded to women, 33% of junior faculty are female, and 11% of senior faculty are female. Gender balance remains elusive.

Witteman *et al.* analysed the results of 23,918 grant applications from 7,093 unique applicants over 5 years across all open, investigator-initiated, Canadian Institutes of Health Sciences grant programmes from 2011 to 2016. When the review focused on the quality of the proposed science, the gap was negligible, but when the review focused on the principal investigator, the gap was 4.0% in favour of male principal investigators. Similar data have been reported in the USA, the Netherlands and Sweden.

Whilst one could argue that a 4% difference is small, these data show that biases (often unconscious) remain. The authors suggest that training of reviewers improves balance. The Wellcome Trust data show that whilst 75% of senior awards are held by men, awards are offered to men and women in equal proportion. By highlighting these issues and understanding why lack of gender balance happens, hopefully we can change behaviours to ensure the best science is funded, regardless of who is submitting the proposal.

Read the full article in *bioRxiv* doi:10.1101/232868

CLINICAL ENDOCRINOLOGY

Pulsatility of glucocorticoid hormones in obese pregnancy

Glucocorticoids are essential for fetal growth and organ development. During pregnancy, activation of the hypothalamic-pituitary-adrenal (HPA) axis drives an approximate threefold increase in serum cortisol concentrations compared with non-pregnant levels. Dysregulation of the HPA axis is associated with pregnancy complications and, in obese pregnancy, reduced HPA axis activity is associated with increased birthweight and prolonged gestation. Circadian (daily) regulation of the HPA axis is maintained in pregnancy, but whether ultradian (hourly) regulation of cortisol pulsatility changes across gestation is not known.

Stirrat *et al.* measured cortisol, cortisone, corticosterone and 11-dehydrocorticosterone in timed serum and interstitial fluid samples to investigate ultradian rhythms of glucocorticoid secretion across gestation in lean and obese pregnancies. They found that total daytime circulating maternal cortisol levels were increased with advancing gestation in lean but not in obese pregnancies. Notably, analysis of interstitial fluid cortisol levels identified that, compared with lean pregnancy, cortisol pulse frequency was significantly lower in obese pregnancy with advancing gestation.

These findings represent a novel mechanism that may explain decreased HPA activity in obese pregnancy.

Read the full article in *Clinical Endocrinology* doi:10.1111/cen.13548

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Lessons from missed central hypothyroidism

Glyn *et al.* describe the case of a 57-year-old woman who became unwell after a total thyroidectomy for management of Graves' disease. She subsequently underwent numerous investigations and treatments over 20 years for a constellation of symptoms including myopathy, arthropathy, pericardial effusion, bilateral ptosis with impaired renal function, thyrotrophin (TSH) 2mIU/L, creatine kinase >1000IU/L and cholesterol 12.5mmol/L.

An astute clinical biochemist reviewed this patient's history and blood results, added on free thyroid hormones and identified profound central hypothyroidism: free thyroxine (fT4) <0.4pmol/L (normal range (NR) 12–22pmol/L), free triiodothyronine <0.3pmol/L (NR 3.1–6.8pmol/L) and TSH 2mIU/L. Thyroxine was started (25µg/day) and slowly titrated over a year. Her symptoms improved and other biochemical indices normalised.

This case highlights the importance of reviewing fT4 as well as TSH, but raises the issue of whether this is possible for all thyroid function tests requested nationwide. It demonstrates the importance of introducing thyroid hormones slowly with thyroxine and not reaching for the intravenous liothyronine. It also demonstrates the importance of reviewing all available information and having a curious mind. If the clinical biochemist concerned had not thought about what was happening, this patient may never have had a diagnosis, and the outcome would have been far less successful.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* **12** EDM-17-0112

ENDOCRINE CONNECTIONS

Global DNA methylation and hydroxymethylation in T2D

The global type 2 diabetes (T2D) epidemic cannot be explained by genetics alone. Environmental factors, including rapid urbanisation and lifestyle habits, have also contributed to this disease through their ability to modulate the establishment and maintenance of epigenetic modifications such as DNA methylation.

Pinzón-Cortés *et al.* have investigated a lesser known epigenetic change – DNA hydroxymethylation, an intermediary step in DNA demethylation – in peripheral blood DNA of patients with T2D who had good or poor glycaemic control compared with controls.

The levels of both DNA methylation and hydroxymethylation in peripheral blood were increased in T2D patients compared with controls. Interestingly,

upon more detailed analysis, this difference was not found to be present between well-controlled patients and controls. This suggests a direct relationship between chronic hyperglycaemia and cumulative changes in the epigenome. Furthermore, the expression of key genes involved in mediating these epigenetic changes was also altered in patients with poorly controlled T2D.

These findings highlight the importance of maintaining adequate glycaemic control in T2D patients, not only to prevent the development of diabetic complications but also to ensure longer term epigenomic health.

Read the full article in *Endocrine Connections* **6** 708–725



Extracellular vesicles in tissue crosstalk during exercise

The health benefits of exercise are well known. Physical inactivity is associated with impaired metabolic homeostasis, including decreased insulin sensitivity and accumulation of visceral adiposity. Extracellular vesicles (EV) are increasingly recognised as an essential mechanism of intercellular communication and are important carriers of proteins, lipids and nucleic acids in plasma.

Whitman *et al.* used nano-ultra-high-performance liquid chromatography (UHPLC) tandem mass spectrometry to perform deep proteomic analysis of femoral artery plasma samples from healthy male volunteers. These were obtained at rest,

immediately after exercise and 4 hours following exercise (recovery) to identify the exercise-induced EV proteome.

They found that exercise induced a significant increase in proteins associated with a wide range of biological processes, including glycolysis, and that exercise-induced EV homed to the liver. Further, femoral arteriovenous difference analysis identified 35 novel candidate myokines that are released into the circulation independently of classical secretion. Although future functional validation of these myokines is needed, this study demonstrates a new paradigm by which tissue crosstalk during exercise can exert systemic biological effects.

Read the full article in *Cell Metabolism* **27** 237–251

Glucose sensing and an effect of metformin on the microbiome

The type 2 diabetes drug metformin is thought to reduce hepatic glucose production. Here, Bauer and colleagues propose a novel mechanism for this, involving the gut microbiome and its regulation of the sodium glucose co-transporter 1 (SGLT1).

In rats, a glucose load infused into the lumen of the upper small intestine reduced glucose production. This effect was dependent upon SGLT1. Three days of a high-fat diet (HFD) reduced SGLT1 expression in the intestinal mucosa, and thus impaired glucose sensing. Both were restored with metformin pretreatment.

At the same time, the team characterised the microbiome of the upper small intestine. Compared with normal diet, an HFD reduced levels of the *Lactobacillaceae* family, and increased abundance of the *Clostridiaceae*, *Enterobacteriaceae* and *Pseudomonadaceae* families, amongst others. Metformin pretreatment changed the population, increasing the abundance of some *Lactobacillus* species.

When transplanted into HFD recipients, the microbiome of metformin-pretreated donors was associated with increased SGLT1 expression and improved glucose sensing, compared with saline-pretreated donors. This effect was lost when small intestine SGLT1 was knocked down. Here are more reasons to take care of your microbiome!

Read the full article in *Cell Metabolism* **27** 101–117

ACUTE PHYSICIAN WITH ENDOCRINOLOGY AND DIABETES: THE CAREER CHOICE FOR YOU?

WRITTEN BY UMASUTHAN SRIRANGALINGAM



Umasuthan Srirangalingam examines the value and importance of broadening your career while still focusing on the specialty of endocrinology.

WHY DO YOU NEED ACUTE MEDICINE?

On reflection, some of my most memorable endocrine patients have presented to me on the acute medical take. Seeing the patient present, *de novo* and undifferentiated, following as the diagnosis unfolds, can provide an unparalleled buzz. The elderly gentleman, non-specifically unwell, losing weight and with a fever; the young mother found confused at home, who failed to pick her children up from school; the man presenting with shortness of breath and a low calcium...*

Of course, as the vast majority of UK endocrinology and diabetes consultant posts have an acute medical component, acute medical competence is an essential skill for those in specialist training grades, to enhance employability and secure a consultant job. But if you do have a choice, why would you opt to do acute medicine?

'Acute medicine is the equivalent of the "lifestyle modification" I so often advocate for my patients... It's good for me!'

Undoubtedly there is security in the 'ivory tower' of specialty medicine, insulated from the unpredictable variations of the acute medical take. The early starts and late finishes, the intensity of work, the vast number of decisions to be made, the pressure to discharge, being confronted with unknowns – all are much greater on the acute take. However, while specialty medicine, in isolation, may feel safer, I suggest that you would lose some of the variety and colour that keeps medicine appealing and fresh.

Acute medicine is the equivalent of the 'lifestyle modification' I so often advocate for my patients... It's good for me! It unquestionably makes me a better physician. It stretches me, keeps me grounded and more relevant.

Participation allows me to keep abreast of new insights across a broader range of specialties. Endocrinology and diabetes by their very nature are multisystem specialties. The very best endocrine and diabetes physicians that I have seen and worked with have, first and foremost, always been excellent general physicians and, independent of their rank, were invariably on the front line.

Acute medicine provides an excellent environment in which to network, by interacting with colleagues over a challenging case, by ensuring that the patient gets access to specialist input early on, and by knowing whom to contact. That network can pay dividends. Some of my most fruitful collaborations have been struck up along the corridors of the acute medical unit. Joint clinics have been set up, diagnoses have been made, and management strategies have been modified based on chance interaction.

'Rather than being an inconvenient part of service provision, acute medicine should be seen as the pinnacle of what we do. It deserves real enthusiasts to champion it.'

WHY DOES ACUTE MEDICINE NEED YOU?

To be an effective service, acute medicine needs buy-in from all parties: there needs to be commitment to the cause. By participating, the endocrine and diabetes physician will have a greater influence and a say in the development of acute services.

In the era of the multimorbid patient, providing the holy grail of 'holistic care' requires the endocrine and diabetes physician to deliver specialty input, but with an appreciation of a patient's co-morbidities and other treatments. Integrated care is more effectively facilitated by a specialty physician embedded in acute medical services.

And looking to the future, recruiting the next generation of endocrine and diabetes physicians is critical to maintaining the specialty. Our future career choice is often based on meeting an inspirational clinician early in our career whom we aspire to emulate. The erosion of team structures in modern medicine can mean that trainees get only limited exposure to certain specialties, with the consequent knock-on effects in recruitment that we are currently seeing. To recruit the best and brightest talent, trainees need to be exposed to the specialty and to see that endocrinology and diabetes is the *sine qua non* for acute medicine.

ACUTE MEDICINE - THE HEART OF THE HOSPITAL

The load on the acute medical service has undeniably risen, with increasing numbers attending A&E, pressures on beds and hospital flow, patients living longer with multiple complex conditions, and limits on social care provision. Acute medicine, and those who deliver the service, needs to absorb all of these pressures. But great challenges provide great opportunities. These include finding different ways to work, to innovate, to educate frontline staff, to integrate research and, ultimately, to improve patient care. It is incumbent on management to acknowledge these additional challenges and incentivise those who take on these roles.

I believe that the health of the acute medical service is a reflection of the health of the hospital as a whole. I am proud to report that, at University College London Hospitals, the Chief Executive of the Trust, the head of the National Institute for Health Research's Biomedical Research Centre and the Department of Health's Chief Scientific Adviser all regularly take part in the acute medical rota. It sends out a crucial message, and is testament to the importance of this activity and its role in the life of the hospital. Rather than being an inconvenient part of service provision, it should be seen as the pinnacle of what we do. It deserves real enthusiasts to champion it.

UMASUTHAN SRIRANGALINGAM

Consultant Endocrinologist, University College London Hospitals

**These patients were diagnosed with disseminated histoplasmosis causing adrenal insufficiency; insulinoma; and hypoparathyroidism-associated cardiac failure.*

THOSE WHO CAN, TEACH: CAREERS INVOLVING TEACHING IN ENDOCRINOLOGY

WRITTEN BY MARALYN DRUCE



Your career aspirations and options seem more varied than ever. You are more likely to gravitate towards so-called 'portfolio careers' and you may find that, by the end of your training, different roles in medicine are being carried out by different people in new jobs that hadn't really been invented when you were starting out as a medical student.

For previous generations of doctors, no training in specific teaching skills was provided. Now, as one of 'tomorrow's doctors', you are expected to embed teaching into all aspects of your clinical practice and clear standards are outlined for you. You can learn and perfect your approach to teaching, just as for all your other clinical skills.

Every doctor is expected to deliver teaching, whether to medical students, allied health professionals, or postgraduate doctors. You may already be involved in some teaching activities in your current role and you may be considering whether or not to develop these further as a bigger element in your career profile.

WHY DEVELOP YOUR TEACHING ROLE?

There are different reasons why you might wish to develop your teaching. They are all equally valid and they are not mutually exclusive!

If you need to teach

As well as being part of your 'duty' if you are a doctor, you may have been asked to do some teaching by a colleague or senior. Perhaps you are going to organise some bedside teaching for a group of undergraduates in your hospital. Maybe you have been asked to run a problem-based learning session because your supervisor is away, or it could be that you have a particular area of knowledge that you have been asked to give a talk on. You may have offered some interdisciplinary teaching to nursing or other colleagues in allied professions, or perhaps you have just started a new job in which some teaching is required in your contract.

These are great opportunities for trying out different teaching skills and for seeing whether you enjoy it and want to take it further (see Table 1 for entry level opportunities). A good way to enhance your skills at this stage is a basic 'teach the teacher' course. These may be available without charge in your Trust or university, covering the teaching theories, principles and teaching tools you will need to be an effective medical skills teacher.

If you enjoy or choose to teach

Perhaps you love sharing your knowledge and helping others to grow and develop, or perhaps you really like the mechanics of teaching. You may

Table 1. Entry-level opportunities – ways to test the water in teaching.

- Run problem-based learning sessions
- Provide bedside teaching for clinical students
- Organise teaching for a firm of undergraduates
- Give some small group tuition for exams
- Teach in an inter-professional setting, e.g. to nurses
- Initiate some peer learning, such as a journal club
- Participate in assessment
- Attend a 'teach the teacher' course

have developed a particular interest in curriculum design or leadership or assessment – the last of these is an area that many forget or find difficult, but is key to effective learning.

There are plenty of other less 'altruistic' reasons for wanting to teach. It may tick an important 'achievement' box on your CV, may create job opportunities for you or may enhance your consultant or academic job application. In addition, it may just be that you would like to take on a role such as a teaching fellowship to get some 'time out' off the treadmill, for personal development or as an alternative to research.

There are several ways to get a more intensive 'taster' by taking on a job that has a large teaching component (Table 2). One day, you might suddenly find that you have taken on a role or developed your own niche where teaching is central to your identity or your job description and you couldn't imagine doing anything else!

Table 2. Taking things further – examples of 'career' teaching roles.

University:	<ul style="list-style-type: none"> • Anatomy demonstrator • Clinical skills teacher • Communication skills teacher • e-Learning fellow
Teaching hospital Trust:	<ul style="list-style-type: none"> • Clinical teaching fellow • Associate Dean • Director of Education
Independent providers:	<ul style="list-style-type: none"> • Learned societies' education roles • Royal Colleges' education roles, exam development, exam boards • Revision courses and other commercial organisations • Writing for journal-based learning

CAREER PLANNING AND QUALIFICATIONS

It is probably important to state here that this doesn't have to be a career 'plan' in order for it to work for you. There isn't an obvious 'climb' to a clear 'summit', unless that is what you want. You might realise that you have gained fantastic skills in the past that will prove useful to your teaching future, although you might also plan some skills development in advance.

The best things to do are to try out different techniques and get some feedback. Play with different ways of doing things and, if you can bear it, engage in a bit of learning theory. There is an evidence base to use, just as there is for your clinical practice. As you progress, think about ways in which your efforts can be more formally recognised or in which you can do more detailed training (Table 3).

Table 3. Obtaining accreditation and recognition for teaching.

- Teach the teacher courses
- Education conferences for continuing professional development
- In-house accreditation in your institution (usually two modules, e.g. CILT, certificate in learning and teaching)
- Deanery e-learning education modules (free)
- Royal College of Physicians 'accredited educator' programme
- Postgraduate Certificate/Diploma/Masters in Medical Education (often possible part-time or by distance learning, but don't underestimate the workload)
- Fellowship levels of the Higher Education Academy: FHEA, SFHEA, PFHEA
- Membership or Fellowship of the Academy of Medical Educators

In general, teaching may be a great way to add interest to your working week, whether or not you choose to take on the 'label' of educator or even educationalist. Whatever your motivation, developing your teaching skills and roles will broaden your CV and help you to understand your subject better. The key tips are the same as for any other area of career development:

- If something seems interesting, say yes
- If you have said yes, give it your wholehearted enthusiasm and your 'best shot'

- You may never know where the road really leads but that is fine – there doesn't have to be a plan and a route.

As with many things in life, the journey is as important as the destination. However, if you do decide that you know where the road is leading you, feel free to use some of the tips in this article as your SatNav. Good luck!

MARALYN DRUCE

Professor of Endocrine Medicine, Department of Endocrinology, Barts and the London School of Medicine

A CAREER IN PHARMA: IS IT FOR YOU?

WRITTEN BY BEN CHALLIS



Low morale amongst healthcare professionals, coupled with the cloud of uncertainty that looms over the post-Brexit scientific landscape, has led many scientists and clinicians to weigh up the pros and cons of alternative careers. Many may contemplate a career in pharma, but few ultimately decide to take the plunge. This may be due to 'cold feet' resulting from limited exposure to pharmaceutical medicine as trainees and/or the varied perceptions of the 'dark side' that exist (any Ben Goldacre fans?).

The pharmaceutical industry offers a multitude of career opportunities for both basic and clinical scientists across the spectrum of drug development. Many pre-clinical scientists will have colleagues, across all pay grades, who have made a successful and seamless leap from academia to pharma. It is true that their research autonomy may be compromised. However, for many scientists stepping off the academic funding carousel, this sacrifice is a small one, as opportunities to explore new scientific curiosities are presented. Those new to pharmaceutical research and development will find a highly rigorous and innovative research environment defined by 'truth seeking', in order to minimise expensive failures of new medicines in advanced clinical programmes.

The clinician scientist is highly sought after at various stages of traditional drug development. Whilst first-in-man studies that characterise the pharmacokinetic properties of a drug largely remain the realm of clinical pharmacologists, clinicians are an integral part of clinical trial design and execution, pharmacovigilance, marketing and medical and regulatory affairs.

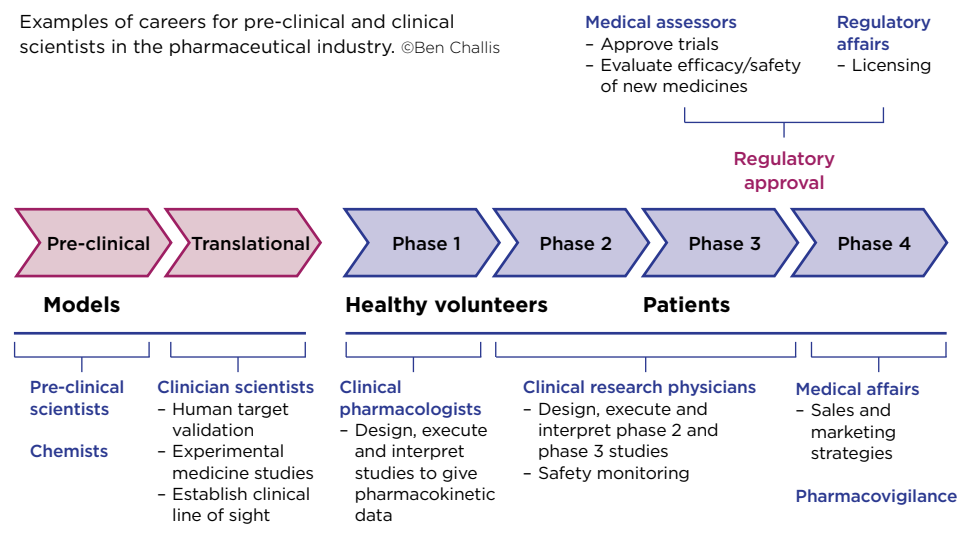
With costs increasing exponentially through each phase of drug development, the pharmaceutical industry continuously strives to lower the attrition rates of new medicines. In the current drug development paradigm, late-stage failure of a medicine is predominantly a result of insufficient efficacy. In order to improve efficiency and increase productivity, it is recognised that successful implementation of early clinical and translational research that provides early validation of a human drug target and improved understanding of human disease mechanisms is necessary.

It is within this context that the skill set of clinician scientists is increasingly valued by pharma. Looking forward, unique and exciting opportunities at the interface between pre-clinical research and development and early clinical development are emerging. Importantly, many pharmaceutical

companies recognise the strategic importance of industry-employed physicians maintaining their clinical competency and knowledge and, in many instances, they encourage medically qualified employees to remain clinically active.

In summary, careers in the pharmaceutical industry are challenging, exciting, highly varied and rewarding. So take the plunge and explore how you can help the 'dark side' to bring important new medicines to the clinic and transform the lives of your patients.

Examples of careers for pre-clinical and clinical scientists in the pharmaceutical industry. ©Ben Challis



BEN CHALLIS

Honorary Consultant Endocrinologist, Addenbrooke's Hospital, Cambridge and Associate Director Physician, Clinical Discovery Unit, Early Clinical Development, AstraZeneca

A DECADE ON: THE SCE IN ENDOCRINOLOGY AND DIABETES

WRITTEN BY MARK GURNELL



Exams are a fact of life – rarely pleasant at the time, but often an essential requirement if you want to get on, especially in a discipline such as medicine. Up until recently, most physicians could comfort themselves in the knowledge that, once they had successfully navigated Parts I & II of MRCP(UK), they wouldn't need to face another exam, before taking up an appointment as a consultant (unless they chose to do so). But then things changed...

In 2008, the Federation of Royal Colleges of Physicians (UK), in conjunction with the relevant specialist societies (in our case, the Society for Endocrinology and the Association of British Clinical Diabetologists) launched the Specialty Certificate Examinations (SCEs), leading to the award of MRCP(UK) (Specialty).¹

Interestingly, the MRCP(UK) website promotes the SCE programme as an opportunity to 'broaden your horizons', although how many trainees view the exam in that light while preparing to sit it could be debated!

However, it is undoubtedly the case that, over the last decade, the SCE has established itself as one of the most respected international postgraduate qualifications. It is in effect a 'quality stamp', providing objective evidence that a specialist trainee has sufficient knowledge of their discipline to practise safely and competently as a consultant.

Perhaps the strongest endorsement of the SCE programme has come from colleagues in other European countries, who are seeking to collaborate with their UK counterparts and build on the expertise and quality of the SCEs. The European Specialty Examination in Gastroenterology and Hepatology is already up and running, and Endocrinology and Diabetes is not far behind. In 2018, the European Society of Endocrinology, in collaboration with the European Union of Medical Specialists (UEMS), will hold the first pan-European Examination in Clinical Endocrinology, Diabetes and Metabolism.

SCE FORMAT

The SCE in Endocrinology and Diabetes runs once a year, typically in early summer. It is a single exam, consisting of two papers, each containing 100 questions. Candidates are allowed 3 hours per paper with a 1-hour break in between. The examination is delivered electronically at designated test centres.

Each question (or 'item') is presented in a standard format (see Panel, above right), with the majority of items based around a brief clinical scenario (the 'stem'), followed by the question (the 'lead-in'), and then a list of five possible answers (the 'options').

Importantly, these options are the 'best-of-five'; i.e. each of the options should be plausible for the clinical context described, but one should be clearly better than the others. This is very different to the historic multiple-choice question papers that many of us sat in the past, when the candidate was often presented with a list of true/false options – several of which were often completely implausible!

Importantly, most of the 200 items seek to test the application of knowledge rather than simple factual recall, thereby attaining the second level of George Miller's classic framework for clinical assessment (Figure), now commonly referred to as 'Miller's triangle'.² In essence, the candidate who successfully navigates the SCE will have demonstrated that they know how to apply the core knowledge relating to their discipline.

Inevitably, critics of such an approach may say that, by settling for an applied knowledge test, the examiners cannot be sure that competence in the SCE inevitably translates into successful/safe clinical practice. However,

Example of the structure of a single best answer question

Stem

A 43-year-old woman has regular palpitations and reports 9kg weight loss over the past 3 months. On questioning, she also admits to poor quality sleep and heat intolerance with occasional headaches. Her resting pulse is 110 beats per minute regular, and blood pressure 150/85 mmHg. She has a fine resting tremor, warm peripheries and a small symmetrical goitre. Visual fields are normal to confrontation testing, and there are no signs of dysthyroid eye disease.

Investigations

Free thyroxine (FT4)	45 pmol/l	(RR 10–20)
Free tri-iodothyronine (FT3)	18 pmol/l	(RR 3.5–6.5)
Thyrotrophin (TSH)	4.8 mU/l	(RR 0.4–4)

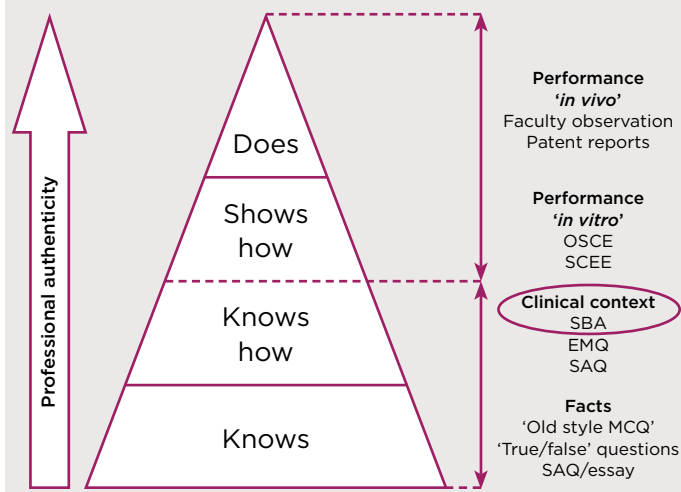
Lead-in

Which is the most appropriate next step in management?

Options

- Arrange contrast-enhanced MR scan of the pituitary
- Arrange thyrotrophin-releasing hormone (TRH) test
- Check serum alpha subunit (ASU) level
- Check serum sex hormone-binding globulin (SHBG) level
- Seek advice on further laboratory analyses

Figure. Miller's triangle: EMQ, extended matching questions; MCQ, multiple choice questions; OSCE, objective structured clinical examination; SAQ, short answer questions; SBA, single best answer; SCEE, simulated clinical encounter examination. Adapted from Miller GE 1990 *Academic Medicine* 65 (9 Supplement) S63–S67



such criticism fails to acknowledge the broader context in which the SCE exists. No trainee is granted a Certificate of Completion of Training (CCT) simply by virtue of passing the SCE. Instead, the SCE is now a compulsory component of the CCT, but satisfactory progression through the ARCP (Annual Review of Competence Progression) process remains the vehicle through which trainees are required to demonstrate their attainment of the higher levels of Miller's triangle (Figure). The SCE seeks to ensure that the underpinning knowledge and its application are secure.

CREATION AND DELIVERY OF THE SCE

As a senior examiner in both the undergraduate and postgraduate arenas, I not infrequently hear candidates complaining that a particular question in an exam wasn't fair, or that the correct answer wasn't included in the five options. My response is usually to smile, politely reassure the concerned students/trainees that the latter is very unlikely, and raise the possibility that perhaps they haven't quite remembered the question properly!

I can do this based on an understanding of just how much time and effort have gone into the creation of each question. Indeed, understanding this process is vital to reassuring candidates that the exam they are about to sit is a high quality assessment, devoid of errors or ambiguity.

The Question Writing Group

Trainees are often surprised to learn just how much time and rigour are involved in perfecting individual questions and in creating an exam containing 200 high quality items. The process begins with individual clinicians being asked to draft questions, which are then subjected to scrutiny by their peers during a 2-day face-to-face meeting.

Such meetings are not for the faint-hearted! It can be quite uncomfortable, watching a question that you are proud of being slowly dismantled. However, if the question survives it almost always emerges a better/more robust item.

In the decade since 2008, the SCE question bank has expanded significantly and many of the items now carry performance data from previous diets, which helps inform the creation of future exams.

'Trainees are often surprised to learn just how much time and rigour are involved in perfecting individual questions and in creating an exam containing 200 high quality items.'

The Exam Board

Each SCE exam is mapped against the SCE Endocrinology and Diabetes blueprint³ which covers the breadth of the Specialty Training Curriculum as published by the Joint Royal Colleges of Physicians Training Board (JRCPTB).⁴

Potential questions for inclusion are reviewed by the Exam Board (comprising at least 10 practising clinicians) at a 2-day meeting. During this review, questions are either accepted in their current format, revised through minor modifications or rejected/returned to the Question Writing Group for more significant revision.

The Standard Setting Group

Once the papers have been finalised, the baton is passed to the Standard Setting Group (SSG) whose job it is to determine the pass mark for the

exam. The SSG includes examiners who have been involved at each step of the process, but also includes 'new faces' who can bring a fresh perspective/critical eye. Ultimately, the final pass mark for the exam is reflective of the judgements of the SSG examiners, linked to the actual performance of the candidates in the exam.

Post-exam analyses

A rigorous psychometric process is followed after each exam, to ensure that the performance of each item and of the exam as a whole is at the expected level, and to allow decisions to be made about poorly performing items.

Inevitably, this takes time, which can be frustrating for candidates who expect a computer-based test to be turned around in a matter of days, if not hours. However, it is vital that these post-examination analyses are completed properly to ensure that the reputation of the SCE as a whole is maintained.

'The fact that significant numbers of European trainees are now keen to sit a 'Europe-wide SCE' based on the UK model/exam speaks loudest for the success of the project.'

CONCLUSIONS

In 2009, when the first SCE in Endocrinology and Diabetes ran, none of us could be quite sure whether the project would be a success and deliver on its stated aims and objectives. As we approach the 10th anniversary, it appears that the SCE is in good health.

Most trainees now accept that achieving the SCE is an important part of establishing their credentials as a bona fide specialist in the field. Indeed, some are keen to point out that they have a badge which many of their seniors don't!

The fact that significant numbers of European trainees are now keen to sit a 'Europe-wide SCE' based on the UK model/exam speaks loudest for the success of the project – it seems UK Endocrinology and Diabetes has created a badge worth having!

MARK GURNELL

Exam Board and Standard Setting Group, Endocrinology and Diabetes SCE

PS Dr Gurnell is happy to provide the correct answer to the example question for anyone who isn't sure...

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WHAT WORKS? WHAT'S GOOD VALUE FOR MONEY? THE ROLE OF NICE FOR THE NHS

WRITTEN BY AMANDA ADLER



The NHS provides care free of charge 'from cradle to grave'. Funded by taxpayers, it must provide them with treatments which work (are clinically effective), but also, because it has limited resources, with treatments that reflect value for money (are cost effective). The NHS cannot spend the same money, at the same time, on (for example) both immunisations and chemotherapy.

This fact, referred to by economists as 'opportunity cost', was expressed clearly in 1999 by Alan Milburn, then Secretary of State for Health, who stated '... the NHS, just like every other healthcare system in the world – public or private – has to set priorities and make choices. The issue is not whether there are choices to be made, but how those choices are made. There is not a service in the world, defence, education or health, where this is not the case.'

THE ROLE OF NICE

NICE, the National Institute for Health and Care Excellence, has a different remit from 'regulators'. It performs this choice-making role for the NHS.

When a pharmaceutical company wishes to sell a new drug or device in the UK, it first seeks marketing authorisation: that is, permission from regulators. Regulators for the UK include the Medicines and Healthcare Products Regulatory Agency and the European Medicines Agency. Regulators require that companies prove their drugs are effective and safe.

Once licensed, many (but not all) drugs are assessed by NICE. Through its Technology Appraisal Programme and independent committees, NICE advises NHS England whether it should provide these drugs to patients.

DIFFERENT DEFINITIONS OF 'EFFECTIVE'

When regulators want to know if a drug for diabetes is effective, it asks the company whether the drug lowers blood glucose. NICE, on the other hand, asks the company **how well** the drug lowers blood glucose **compared with** what the NHS currently offers.

NICE recognises that improving haemoglobin A1c by one unit (and the cost of achieving it) would be impossible to compare with improving, say, the Expanded Disability Status Scale for multiple sclerosis by a unit.

NICE considers that an intervention which improves length-of-life and/or quality-of-life could reasonably be considered to reflect effectiveness across diseases. This underlies the quality-adjusted life year (QALY) and 'cost-utility' analyses. NICE then asks, 'how much would the NHS have to spend – given how many QALYs the new drug is likely to generate – compared with what the NHS currently offers?'

COST EFFECTIVENESS IS MORE THAN PRICE

While a drug's price often drives cost (in)effectiveness, NICE considers all costs. When evaluating a new drug for osteoporosis, NICE would necessarily consider (in addition to the cost of the drug) the cost of fractures averted, and the costs associated with adverse effects, both compared with standard care.

CHALLENGES

Evidence supporting decisions is rarely complete, which forces decision makers to use their best judgement. Some of these challenges are reflected in the following illustrations:

- **Gathering evidence from the right patients:** In 2006, the NICE Technology Appraisal Committee addressed inhaled insulin¹ and considered that it would be best for people averse to using needles. However, the company provided no evidence for this group.

- **Trials in endocrinology infrequently measure whether drugs prolong life**
- **'Cross-over':** In 2017, NICE evaluated everolimus and sunitinib, recommending them as options for treating unresectable or metastatic neuroendocrine tumours (NETs).² NICE encountered a problem: cancer trials commonly include progression of disease as the main endpoint, and permit patients in the control group to switch to the new treatment upon disease progression. For a drug more effective than standard care, this cross-over dilutes its effect on prolonging survival. The Committee concluded '... despite the non-significant overall survival results and high levels of cross-over, both everolimus and sunitinib are clinically effective.'
- **No 'head-to-head' trials:** In the same appraisal, there were no trials comparing everolimus and sunitinib with each other. This required decision makers to compare them indirectly using two trials, each of which compared the active drug with best supportive care (the 'link'). The Committee concluded that everolimus and sunitinib have similar clinical benefits for treating pancreatic NETs. Yet, indirect comparisons generate more uncertainty than evidence from trials comparing treatments directly.
- **Quality of life is not 'naturally' a number, and few trials measure it.**

'NICE helps the NHS allocate resources to maximise health for the greatest number of people.'

WHAT IF A DRUG IS NOT COST-EFFECTIVE?

When NICE does not recommend a drug because of price, the company may offer the drug to the NHS at a (confidential) discount agreed with the Department of Health in a 'patient access scheme'.³ This has inspired many positive recommendations.

CONCLUSION

Many treatments improve on what the NHS offers, but accessing these regardless of cost is not realistic in a publicly funded health system. NICE helps the NHS allocate resources to maximise health for the greatest number of people. NICE depends on people working within the NHS as well as patients, academics and others to carry out its work. If you are interested, you will find information here: www.nice.org.uk/get-involved.

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EARLY CAREER PRIZE LECTURE

INSIGHTS INTO GPCR TRAFFICKING AND BIASED SIGNALLING BY STUDIES OF CALCIUM HOMEOSTASIS

WRITTEN BY CAROLINE GORVIN



Caroline Gorvin provides a synopsis of her Early Career Prize Lecture, covering work during her time as a Post-Doctoral Researcher at the Academic Endocrine Unit, University of Oxford.

Extracellular calcium (Ca^{2+}_e) is essential for the regulation of a multitude of biological functions, including mineralisation of bone matrix, neuromuscular excitability and blood coagulation, as well as for maintaining intracellular calcium (Ca^{2+}_i) stores that are required for functions ranging from muscle contraction to hormone secretion.¹

The calcium-sensing receptor (CaSR) is a G protein-coupled receptor (GPCR) that plays a fundamental role in maintaining calcium homeostasis by sensing the Ca^{2+}_e level in the blood and regulating the synthesis of parathyroid hormone (PTH) to control this.²

Ca^{2+}_e binds directly to the CaSR, which leads to receptor conformational changes that mediate GDP-to-GTP exchange at associated G proteins, and initiate downstream signalling pathways. The CaSR is able to couple to a variety of G proteins, but predominantly to the $G_{q/11}$ and $G_{i/o}$ families, which activate signalling including initiating Ca^{2+}_i mobilisation from the endoplasmic reticulum, activating mitogen-activated protein kinase (MAPK) pathways and reducing cyclic AMP (cAMP) production.²

STUDYING CaSR MUTATIONS

Much of what has been learnt about the CaSR comes from studies of patients with mutations in the receptor. In the majority of cases, patients with heterozygous loss-of-function mutations of the CaSR have familial hypocalciuric hypercalcaemia (FHH), while patients with heterozygous gain-of-function mutations have autosomal dominant hypocalcaemia (ADH). Although benign in most cases, CaSR mutations can cause muscle

cramps, kidney stones, chondrocalcinosis and seizures in some patients. Characterisation of the effect of these disease-causing mutations *in vitro* has demonstrated that they may influence CaSR signalling responses in a biased manner, with some FHH mutations switching the wild type CaSR from preferentially coupling to Ca^{2+}_i to a mutant receptor that signals predominantly by MAPK, or equally via the Ca^{2+}_i and MAPK pathways. In contrast, many ADH mutations cause a signalling bias by coupling more strongly to Ca^{2+}_i .³ However, the molecular mechanisms that mediate this signalling bias are often unclear.

THE Arg680Gly MUTATION

In our studies, we identified an ADH-associated mutation which affects the Arg680 residue of the CaSR, which is located within the third transmembrane domain of the receptor.⁴ Using *in vitro* analyses, it was shown that, in contrast to other ADH mutations, Ca^{2+}_i signalling is not affected by the Arg680Gly mutation, and that it instead enhances MAPK signalling (Figure). This increased MAPK signalling did not arise from G protein-dependent pathways, investigated by blocking each G protein pathway using specific inhibitors, but involved a β -arrestin specific pathway. This β -arrestin-mediated pathway does not function at physiological concentrations of Ca^{2+}_e in wild type CaSR-expressing cells.

Using a homology model of the CaSR built with the structure of the related GPCR, mGluR1, and engineered mutants of the CaSR, it was demonstrated that the Arg680 residue forms a salt bridge with an adjacent residue on the second extracellular loop of the CaSR. This salt bridge

maintains the CaSR in an inactive conformation, and the Arg680Gly ADH mutation disrupts this salt bridge, probably allowing greater flexibility between the cytoplasmic regions of the CaSR transmembrane domains, and facilitating β -arrestin binding, which acts as a scaffold for MAPK signalling components.

These studies have, therefore, demonstrated a novel signalling pathway, which may be exploited for the development of new treatments for patients with mutations in the CaSR, or other GPCRs.

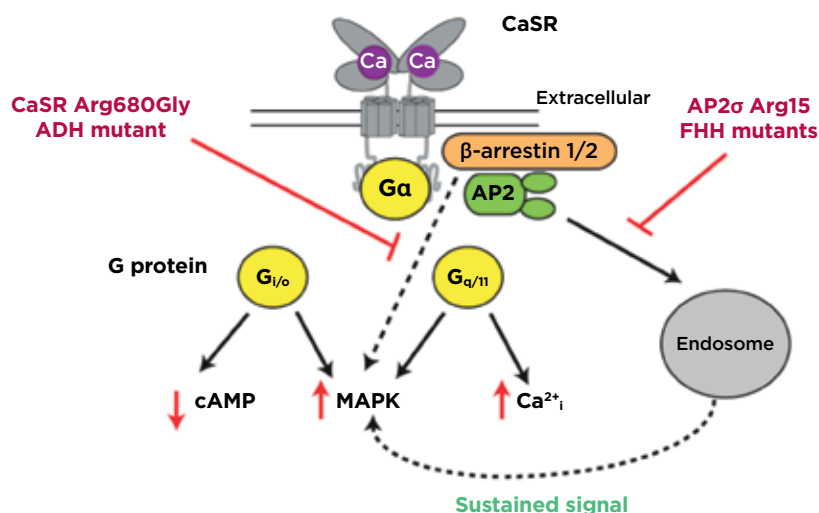
MUTATIONS IN OTHER GENES

In addition to CaSR mutations, studies of hypercalcaemic patients have demonstrated that FHH may arise from mutations in other genes.

Interestingly, mutations in a subunit (the σ -subunit) of the adaptor protein-2 (AP2), which is ubiquitously expressed, also give rise to FHH.⁵ AP2 is a heterotetrameric protein that plays a fundamental role in clathrin-mediated endocytosis, a process which is required by cells for nutrient uptake and internalisation of transmembrane cell surface proteins, such as GPCRs. The AP2 σ protein is the smallest subunit of the AP2 complex, and mutations identified in FHH patients affect a single residue, Arg15.

Previous studies have shown that the AP2 σ Arg15 residue is important for binding to specific regions

The CaSR can activate G protein-signalling pathways downstream of the G proteins $G_{i/o}$ and $G_{q/11}$, leading to reductions in cAMP, and increases in Ca^{2+}_i and MAPK. Studies of the ADH CaSR mutant, Arg680Gly, demonstrated that the CaSR can also activate MAPK signalling using β -arrestin. Regulation of CaSR expression at the cell surface is controlled by clathrin-mediated endocytosis that involves AP2. Studies of the FHH-associated AP2 σ Arg15 mutations revealed the CaSR can signal from within the cell following endocytosis (sustained signal). ADH, autosomal dominant hypocalcaemia; AP2, adaptor protein-2; CaSR, calcium-sensing receptor; FHH, familial hypocalciuric hypercalcaemia. ©Caroline Gorvin



(dileucine motifs) of transmembrane proteins.⁶ It was therefore hypothesised that FHH mutations in Arg15 must affect binding of AP2 σ to the CaSR, and thus affect CaSR internalisation. Indeed, studies of CaSR trafficking using total internal reflection fluorescence microscopy demonstrated an impairment of CaSR endocytosis in cells expressing FHH-associated AP2 σ mutations, and consequently increased CaSR cell surface expression.⁷ However, AP2 σ mutations reduce CaSR-mediated signalling by both G_{q/11}- and G_{i/o}-mediated pathways. This at first appeared paradoxical, as more receptor at the cell surface should equate to more signalling by the receptor. So, how are the AP2 σ mutations impairing CaSR signalling?

ELUCIDATING THE MECHANISM

To uncover the molecular mechanisms, we turned to other GPCRs as a guide. Some GPCRs, including the receptors for thyrotrophin, PTH and luteinising hormone, can continue to signal once internalised.⁸ We hypothesised that the CaSR may also have long-lasting signals from within the cytoplasm, and that depletion of internalised CaSR by the FHH-associated AP2 σ mutations would reduce signalling from this source.

Using a combination of imaging techniques, signalling assays and inhibitors of endocytosis, it was demonstrated that the CaSR can signal from an internal location that is likely to be endosomal (Figure).⁷ Furthermore, this internalisation-dependent pathway involves only G_{q/11} signalling,

and therefore these studies have shown how a single GPCR can resolve pleiotropic signals by spatially directing G protein selectivity.

Elucidation of these novel CaSR signalling pathways has uncovered new mechanisms by which the receptor signals, and may help facilitate the development of targeted therapies to activate β -arrestin-mediated or sustained endosomal signalling in a biased manner.

CAROLINE GORVIN

Senior Research Fellow, Institute of Metabolism and Systems Research, University of Birmingham

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EARLY CAREER PRIZE LECTURE A ROLE FOR HYPOXIA IN MENSTRUAL PHYSIOLOGY AND PATHOLOGY

WRITTEN BY JACKIE MAYBIN



Jackie Maybin provides a synopsis of her Early Career Prize Lecture on hypoxia in menstrual physiology and pathology.¹

The presence of endometrial hypoxia at the time of menstruation was suggested over 70 years ago, but has remained a topic of intense debate ever since. Determining the presence and role of hypoxia in menstrual physiology will increase our understanding of the mechanisms of repeated, scar-free, endometrial injury and repair which occur monthly during a woman's reproductive lifetime. In addition, it may identify new therapeutic strategies for women suffering from common and debilitating menstrual disorders.

A CLINICAL PROBLEM

One in three women will experience heavy menstrual bleeding (HMB) during their lifetime. HMB can result in severe anaemia and has a significant negative impact on quality of life. It is estimated that 5 million work days are lost each year in the UK due to menstrual problems, resulting in a huge socio-economic cost.

Current medical therapies have many hormonal side effects, meaning otherwise healthy women are proceeding to risky, fertility-removing surgery. There is a clear unmet need for new medical treatments. These

can only be developed by delineating endometrial physiology and identifying the aberrations that occur in women with HMB.

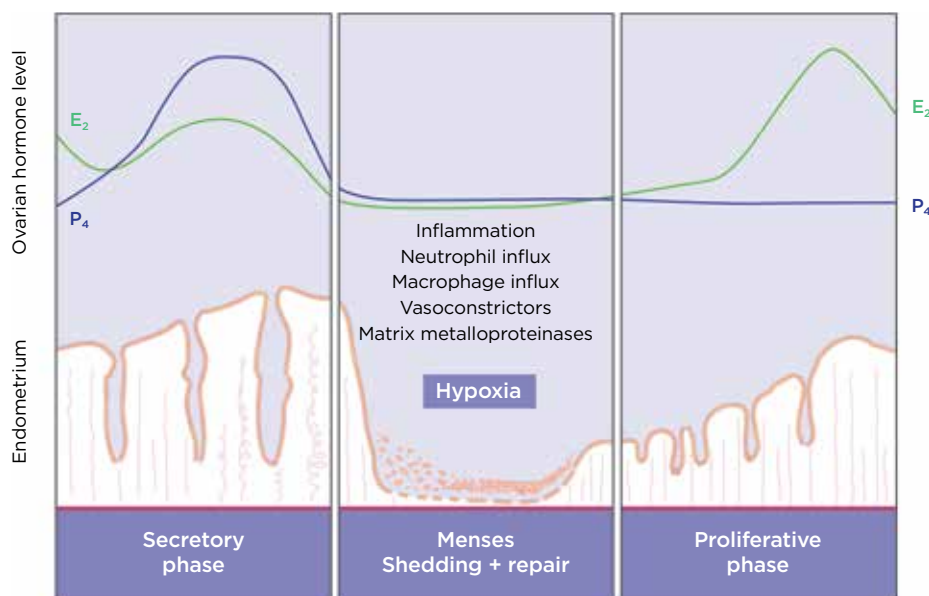
THE PHYSIOLOGY OF MENSTRUATION

In the absence of pregnancy, the corpus luteum regresses and there is a dramatic decline in progesterone levels. This progesterone withdrawal is the trigger for menstruation (Figure). There is an increase in endometrial inflammatory mediators and an influx of innate immune cells to the local environment. Vasoconstrictors are also increased at this time, including prostaglandin F₂ α and endothelin-1, to reduce endometrial arteriole diameter and limit menstrual blood loss.

This endometrial inflammatory cascade culminates in activation of matrix metalloproteinases. These enzymes degrade the extracellular matrix, initiating shedding of the upper two-thirds of the endometrium during menstruation. The resulting denuded endometrial surface must repair efficiently to limit menstrual blood loss and to regain endometrial function, i.e. facilitate implantation if fertilisation occurs. The regulation and mechanisms of this repeated, scar-free, endometrial repair are not well understood.

THE PRESENCE OF HYPOXIA IN THE ENDOMETRIUM

In the 1940s, Markee transplanted human endometrial tissue into the anterior chamber of the rhesus monkey eye. This allowed direct



The human menstrual cycle. A sharp decline in progesterone levels (P_4) triggers an inflammatory response within the local endometrial environment, culminating in menstruation. Intense vasoconstriction of the specialised spiral arterioles results in a transient endometrial hypoxia, which drives the repair processes necessary to limit menstrual blood loss. E_2 , estradiol. ©Jackie Maybin

visualisation of endometrial changes after administration of progesterone and subsequent withdrawal. Intense vasoconstriction of endometrial spiral arterioles was visualised, compatible with tissue hypoxia following progesterone withdrawal.²

However, since this observation, the presence and role of hypoxia in the endometrium have remained the subject of debate in the reproductive literature. *In vitro* culture of primary stromal cells and *ex vivo* culture of endometrial explants revealed that hypoxia did not increase levels of matrix metalloproteinases, suggesting that hypoxia is not involved in endometrial breakdown.^{3,4}

A mouse xenograft model also failed to detect hypoxia during endometrial breakdown or repair. In this model, fragments of functional endometrium were xenografted to ovariectomised, immunodeficient mice, which were then exposed to sequential oestradiol and progesterone prior to withdrawal of ovarian hormones.⁵ However, disturbance of endometrial vascular architecture and the immunodeficiency necessary for maintenance of this model will have had a considerable impact on menstrual physiology.

We hypothesised that hypoxia was present in the menstrual endometrium and that it is necessary for normal endometrial repair of the denuded endometrial surface following shedding.

We examined well-categorised human endometrial tissue collected from women at different stages across the menstrual cycle. Hypoxia inducible factor (HIF) is the master regulator of the cellular response to hypoxia. It is composed of two subunits: alpha (HIF-1 α) and beta (HIF-1 β). HIF-1 α is regulated by oxygen and is rapidly degraded by the proteasome in normoxic conditions. Therefore, its presence is a marker of hypoxia. We revealed that HIF-1 α is present in the human endometrium exclusively following progesterone withdrawal, with maximal levels during menstruation. Downstream targets of HIF-1 α were also increased in the endometrium during menstruation.

To confirm the presence of hypoxia at menstruation, we artificially induced mice to have periods by giving them injections of oestrogen and progesterone to mimic the hormone fluctuations experienced by women. Pimonidazole (HydroxyprobeTM) is a marker that detects tissue oxygen levels below 10mmHg. Pimonidazole staining was present in the endometrium of mice during active menstrual bleeding, but had completely resolved when endometrial repair was complete.

HYPOXIA'S ROLE

Our human and mouse studies detected hypoxia in the menstrual endometrium; but what role does it play in endometrial function? Women with HMB had significantly less endometrial HIF-1 α protein during menstruation than women with normal blood loss. This is consistent with a defective hypoxic response. Similarly, women with HMB did not have the increase in HIF-1 α downstream targets at menstruation that was seen in those with normal bleeding. Women with HMB bled for 2 additional days, consistent with delayed endometrial repair.

To define the role of endometrial hypoxia, we prevented its occurrence in our mouse simulated menses model, by placing mice in hyperoxia (75% O_2) during menstruation. This resulted in reduced endometrial HIF-1 α and delayed endometrial repair. HIF-1 α heterozygote mice are phenotypically normal, but are unable to mount an appropriate HIF-1 response in hypoxia. Simulation of menses in these mice also resulted in significantly delayed endometrial repair.

As our human studies suggest that women with HMB have a defective hypoxic response in their endometrium during menses, we utilised our mouse model of non-hypoxic menstruation to investigate novel therapeutic strategies. Dimethyloxylglycine (DMOG) is a pharmacological agent that stabilises HIF-1 α , even in the presence of oxygen. DMOG administration during menstruation restored normal endometrial repair.

CONCLUSIONS

This study reveals for the first time that hypoxia is required during menstruation to optimise endometrial repair. Increasing HIF-1 at menses shows real promise as a novel, non-hormonal medical treatment to limit menstrual blood loss.

JACKIE MAYBIN

MRC Centre for Reproductive Health, University of Edinburgh

This research has been published as Maybin JA et al. 2018 Nature Communications doi:10.1038/s41467-017-02375-6.

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'FEMINISM' – STILL AN ENDOCRINE ISSUE?

WRITTEN BY VICTORIA SALEM

Merriam-Webster, publisher of America's leading dictionary, announced that its most searched-for word of 2017 was 'feminism'. After years of believing that we had reached a 'post-feminist' position of equality, President Trump had saved us from this false reverie. Indeed, whatever your opinion is on the recent outpouring of sexual harassment allegations that have unseated high profile public figures, the new wave of feminism can hardly have passed you by.

Of course, we endocrinologists needn't worry ourselves about such concerns. The Society for Endocrinology reports that 44% of its membership are women. In terms of UK clinical trainees, we reached gender parity in the specialty of endocrinology and diabetes some time ago, and now our consultant body is also equally distributed.¹ Moreover, endocrinologists are often the most satisfied/least burned-out in surveys of work-life balance amongst clinicians.²

On the other hand, the Society doesn't make records of what proportion of its professorial membership is female. Quickly scanning the professors of endocrinology at universities in London suggests that the figure remains steadfastly below 20%. This is despite more than enough time having elapsed since women outnumbered men at medical graduate level to have seriously altered that proportion. More broadly, a similar proportion (<20%) of newly elected fellows to the Royal Society or successful Wellcome Trust Senior Investigators are female.³ Once again, in 2017, women were seriously under-represented in new NHS Clinical Excellence Awards.⁴

'Probably unconsciously, the characteristics of successful academics – competition, self-promotion, aggression – are less common and/or tolerated in women.'

On the assumption that 'success' is commensurate with national recognition on pay scales, or rising up the academic career ladder to international research prominence, we should ask why women continue to fall behind men.

WHY DOES THE LEAKY PIPELINE STILL EXIST?

In a recent discussion which I convened with postdocs at Imperial College London, we did not detect a lack of ambition or opportunities for women. However, there was a debate whether the ability/willingness to succeed in such a competitive system was a prerequisite for success, and whether a gender bias was inherent in this.

Women still take on most of the family caring responsibilities, and very young children, even if only temporarily, have a tendency to alter career priorities enough to deal a fatal blow to one's competitiveness.

Indeed, the view that the culture of scientific research favours men over women was more strongly expressed by Imperial's senior female academics,

who describe power and social capital still primarily in the hands of men. This may explain why the pipeline remains leaky, even for women who have not taken time off to raise a family.

Probably unconsciously, the characteristics of successful academics – competition, self-promotion, aggression – are less common and/or tolerated in women. Women still ask far fewer questions at scientific conferences (watch this space for the results a study of the gender discrepancies in the number and style of questions asked at last year's Society for Endocrinology BES conference!). They ask for less money too – reflected in the persistent wider reports of academic gender paygaps.⁵

'We should be wary that there is still work to be done, but proud of what our specialty has achieved.'

WHAT ARE WE DOING ABOUT IT?

We all have a responsibility to be feminists, as part of our opposition to other systemic oppressions that still pervade our culture: racism, classism and homophobia.

In academia, the Athena SWAN (Scientific Women's Academic Network) movement has suffered the ironic accusation that the immense administrative load that came with it was disproportionately disadvantageous to the female academics who were leading it.⁶ Dame Sally Davies' decision to insist that medical schools must have an Athena SWAN Silver Award to apply for National Institute for Health Research funding provoked some cynicism, but in reality it has resulted in immense change.

Look at what your local Athena teams have done: mentoring schemes, improving the visibility of female role models, postdoc career development initiatives, carers' funds for travel to conferences, work/life balance panels, gender pay reviews, gender-balanced promotions panels and unconscious bias training, to name but a few.

Endocrinologists play central roles in such teams across the country (Barts, Brunel, Brighton, Edinburgh and Imperial, amongst many others). We should be wary that there is still work to be done, but proud of what our specialty has achieved.

VICTORIA SALEM

Senior Clinical Research Fellow, Diabetes and Endocrinology, Imperial College London, Hammersmith Hospital

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SIX IMPOSSIBLE THINGS BEFORE BREAKFAST

BRINGING ENDOCRINE SENSIBILITY TO ACUTE MEDICINE



Due to the unique and puzzling intricacies of the junior doctor contract, whilst I was on the wards in the latter half of December, the rota adopted 'advent tendencies', with each day revealing a new team to share the seasonal cheer on the ward.

Against the odds, this was a sociable and heartening experience, driven almost entirely by the boundless enthusiasm and energy of the younger doctors who still fill our hospitals. Smiling, even-tempered, tireless, they even offered me chocolate when I sighed too heavily at troubling blood tests and X-rays.

We had bonded and spent time working hard in a febrile environment, so towards the end of the day I did my 'Let's-ask-about-future-careers' routine.

'So have you ever thought about training/specialising in diabetes and endocrinology when you finish core training? You should think about it – you are bright/energetic/personable/capable.'

Awkward silence, shoe gazing, more chocolate proffered.

Something I said? Well, the responses varied...

'You never seem to get anyone better – they just keep coming back.'

'I have no idea what you really do as I've never been to your clinic.'

'Don't you get fed up just helping out specialties who do all the interesting stuff?'

'Your SpRs [specialist registrars] do loads of the general medicine.'

So, how come the youth of today seem to have gone off what I, and others, considered the only sensible choice of career all those years ago?

Regrettably, the sentiments expressed by my junior colleagues are nothing new to many of us, but are these smart young doctors mistaken in their beliefs or just coolly interpreting the evidence presented to them? And are we hearing what they are saying?

There is a wonderful passage in *Alice Through the Looking Glass*, where Alice cries out in desperation when she is asked to believe the fanciful age of the White Queen.

'There's no use trying,' she said: 'one can't believe impossible things.'

'I daresay you haven't had much practice,' said the Queen. 'When I was your age, I always did it for half-an-hour a day. Why, sometimes I've believed as many as six impossible things before breakfast.'

The National Health Service is often fantastic and fantastical in equal measure and, unlike Alice, I think many of us are well versed in rewriting the narrative into whatever it takes to get through the day. However, if we want to change our situation, we have to start believing we can do so. When it comes to training, that means cutting loose of the unhappy current reality and moving to 'what needs to be' rather than 'what is', and starting to make changes.



Alice and the White Queen, from *Through the Looking-Glass and What Alice Found There*. Illustration by John Tenniel (Public Domain)

Let's start with the easy ones and, in particular, that hoary chestnut about physicians involved in long term conditions being nothing more than overpaid chroniclers of natural decay. Enough already. We can and do make a difference all the time, enabling people to live their best lives for as long as possible. We do so using an ever-increasing armamentarium of drugs, pens, pumps, meters and sensors, and we provided ambulatory care in endocrine day units for decades before it was re-discovered as a magic cure for overcrowded hospitals. We are not bashful handmaidens, mopping the furrowed brows of those undertaking real work, but have the fortunate position of being able to orchestrate a whole range of multidisciplinary teams.

So, how come all of this appears to be happening in a hidden valley behind a waterfall, beyond the currently imagined world of our junior colleagues? You cannot fall in love with something you have never seen. Winter pressure is now routine crisis, and the focus on flow above all else makes time off the wards virtually impossible.

When I trained in the starched white coat days of 6 months of surgery, 6 months of medicine, I still managed to get to departmental educational

'To bring that endocrine sensibility to acute medicine, one needs to have been given the opportunity to train in the discipline in the first place.'

meetings and talks. Many of us attended clinics as Senior House Officers. Different times need different solutions. If we can have FY1 positions in haematology, intensive care and psychiatry, why not an FY1 in diabetes and endocrinology, based wholly and only in that speciality for 4 months with no acute takes and no general internal medicine (GIM), but based in clinic and being a part of the referral and outreach team?

Finally, there's the biggest challenge to SpR training (GIM). Many say we are a key link to the front door general team. As a specialty, we are both willing and able to enter the fray here. But to be able to bring that endocrine sensibility to acute medicine, one needs to have been given the opportunity to train in the discipline in the first place, and this cannot happen while being elsewhere for long periods of time.

This is not shirking responsibility, but an essential need to propagate the next generation of endocrinologists. Training requires the time to acquire 'clinic craft' as well as 'ward craft', perhaps even more so in a discipline like ours, where the bulk of our specialty work is carried out in the outpatient setting. Just as surgeons need operating time, so our trainees need clinic time.

This is not to say that folk should not enjoy a thriving 30-year career, combining acute medicine with outpatient practice, but the training that launches this has to be right in the first place. However appealing it is in the short term, allowing more generic service to continually occupy the space where specialist training needs to be could mean there will be no specialist service at all in the future.

It is our responsibility to make changes now, by being imaginative and not worn down by the current pressures, by developing post-CCT (certificate of completion of training) posts if necessary, so we have the highly skilled diabetologists and endocrinologists of the future.

TONY COLL

Wolfson Diabetes and Endocrine Clinic, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge



Endocrine NETWORKS

Enabling communication, collaboration and knowledge sharing

Endocrine Networks provide dedicated forums across specialty areas within endocrinology. The Networks enable you to communicate with members with similar interests, share best practice, exchange ideas and collaborate on cross-disciplinary research initiatives in Endocrinology.

Grow your NETWORK

Current Networks

- **Adrenal and Cardiovascular** – network convenors are Jeremy Tomlinson and Scott MacKenzie
- **Bone and Calcium** – network convenor is Jeremy Turner
- **Endocrine Neoplasia Syndromes** – network convenors are Raj Thakker and Paul Newey
- **Metabolic and Obesity** – network convenors are Barbara McGowan and Kevin Murphy
- **Neuroendocrinology** – network convenors are Waljit Dhillon, Márta Korbonits and Giles Yeo
- **Reproductive Endocrinology and Biology** – network convenors are Stephen Franks and Andrew Childs
- **Thyroid** – network convenors are Petros Perros and Carla Moran

Join your network online
www.endocrinology.org



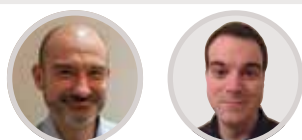
Taking a closer look: ENDOCRINE NETWORKS

The Endocrine Networks enable members of the Society for Endocrinology to share knowledge and best practice in order to find solutions to challenges within their specialist field. Seven Endocrine Networks provide a platform for collaboration for basic and clinical researchers, clinical endocrinologists and endocrine nurses.

MEET YOUR ENDOCRINE NETWORKS CONVENORS

Adrenal and Cardiovascular

Jeremy Tomlinson Oxford
Scott MacKenzie Glasgow



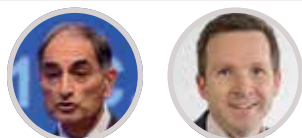
Bone and Calcium

Jeremy Turner Norwich



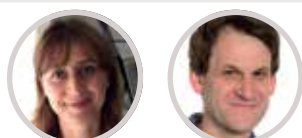
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Raj Thakker Oxford
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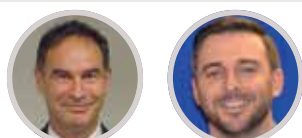
Neuroendocrinology

Waljit Dhillon London
Márta Korbonits London
Giles Yeo Cambridge



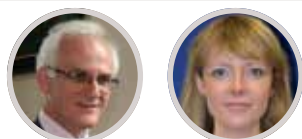
Reproductive Endocrinology and Biology

Stephen Franks London
Andrew Childs London



Thyroid

Petros Perros Newcastle upon Tyne
Carla Moran Cambridge



NEW ENDOCRINE NETWORK MEETINGS

The Endocrine Networks provided an innovative forum for discussion and collaboration at the Society for Endocrinology BES conference in 2017.

These 'Endocrine Network Research Incubator Meetings' gave Network members the chance to present their fledgling research ideas to a panel of experts and audience participants. Constructive advice from the experts and suggestions from the audience will help get their new ideas off the ground.



COULD YOU BENEFIT FROM AN ENDOCRINE NETWORKS GRANT?

These grants of up to £5,000 support the activities of Endocrine Network members. You can use them for many activities, such as:



Co-ordinating cross-institution and collaborative initiatives, such as grant applications to funding bodies



Running an event



Employing a local institution member of staff to set up a database

HOW TO APPLY

Applications are accepted throughout the year (there are no deadlines) and must be made via your Endocrine Networks convenor. To contact your convenor, email grants@endocrinology.org. For more information see www.endocrinology.org/grants-and-awards/grants/endocrine-network-grant.



Visit the Endocrine Network webpages at www.endocrinology.org/membership/endocrine-networks for the latest news, events and highlights from your networks. Do you have something to share? Send your suggestions to rachel.austin@endocrinology.org.



Public Engagement Training Workshop

Tuesday 17 April 2018

The Hilton
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- Find your own voice to communicate endocrinology better with the public
- For nervous novices through to confident speakers
- Learn from a mixture of theory, principles and practical exercises
- Discover how to simplify your research to be accurate, memorable and engaging



Learn from Tom Pringle (aka Dr Bunhead), who has trained thousands of people to communicate their passion for research, drawing on his experience performing in venues the world over, from grand opera houses to science classrooms.

Free for members
Travel expenses will be reimbursed



The scientist and the spoonful of sugar...

FUNDED BY A SOCIETY PUBLIC ENGAGEMENT GRANT

Public engagement is becoming a vital part of everyday life for a scientist. People are genuinely interested in what goes on in research laboratories, want to know how taking part in clinical trials can be beneficial, and are curious about what research funding actually pays for. Additionally, our funders increasingly require evidence of participation in public engagement events.

The Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM) has been actively involved in public engagement at small, local events for the last few years. These events have given us the opportunity to test out ideas and have convinced us that involvement in such activities is beneficial and enjoyable.

Consequently, we decided that we needed something more visually captivating to attract more attention. With this in mind, we applied for and were awarded a Society for Endocrinology Public Engagement Grant to fund the purchase of a new gazebo – complete with departmental logos and departmental research images. This ensured our stall was clearly visible at events in 2017, and that it will remain prominent at many future events. In addition to the gazebo, we were able to purchase hands-on anatomy models and craft items to help us educate event attendees about endocrine organs and function.

OCDEM attended several public events over the summer of 2017, including the Oxfordshire Science Festival, the Headington Festival and the Royal Society Summer Science Exhibition. At these events, we focused on educating the public about nutrition, lifestyle choices and the causes of diabetes. Using the gazebo and materials funded by the grant we were able to run a variety of games and activities designed to help the public understand these endocrine concepts in a fun and engaging way.

Amanda Bennett. ©Kate Lines and Marco Pontecorvi



Katherine Owen. ©Kate Lines and Marco Pontecorvi



Nathan Denton. ©Kate Lines and Marco Pontecorvi

Feedback from the public has been overwhelmingly positive, and convinced us that continued participation in such events is important, not only for educating visitors about our work, but also in helping us to gain new perspectives that enhance our future research. The award of this Society for Endocrinology Public Engagement Grant has ensured that this will be a possibility for years to come.

CAROLINE GORVIN
University of Oxford

Do you have a great idea for an outreach project?
Find out how you can apply for a Society Public Engagement Grant at www.endocrinology.org/grants-and-awards/grants/public-engagement-grant.

Next deadline: 28 March 2018

Could you be an **ENDOCRINE AMBASSADOR?**



REPRESENT THE MANY FLAVOURS OF ENDOCRINOLOGY

©Shutterstock

Do you want to increase interdisciplinary collaborations at your institution? Could you help to raise the profile of endocrinology, and inspire those working in intersecting fields to identify with the discipline? Then represent the Society for Endocrinology at your institution by becoming an Endocrine Ambassador!

As an Endocrine Ambassador, you'll be your institution's champion for endocrinology, bringing the many different flavours of our discipline together, and you'll encourage students and colleagues to join the Society.

Funding is available to ambassadors on a first come, first served basis, to support a small event aimed at encouraging interdisciplinary collaborations and recruiting new members to the Society.

Nigel Page hosted the first sponsored Endocrine Ambassador event at Kingston University, London. It featured a guest lecture by Gary Frost (Imperial College London) on 'Fermentable carbohydrate-driven appetite regulation in the brain'.



Nigel Page, Director of Learning and Teaching at the School of Life Sciences, Pharmacy & Chemistry, Kingston University London, who is a Society Endocrine Ambassador and Public Engagement Committee member, tells us more about being an Endocrine Ambassador.

For many years I was the informal contact for the Society at Kingston, and encouraging new members to engage with the Society was a big part of that. One year, I even received the Society's accolade for recruiting the greatest number of new members, as well as helping to recruit some of the first students to the Society's Student Ambassadors Scheme! So, when the opportunity came along to become an official Endocrine Ambassador and to champion endocrinology within my institution, I took it.

Kingston has several interdisciplinary research groups, including those involved in diabetes, cancer, drug discovery and delivery, sports science, and



'Being an Ambassador has certainly afforded me the opportunity to get more people involved, to stimulate debate, and hopefully to convince a few more people of the benefits of being part of the endocrinology community via the Society.'

nutrition. With the funding opportunities offered to Endocrine Ambassadors, we could organise an event to bring together many of the different flavours of our endocrinology community. Overall, being an Ambassador has certainly afforded me the opportunity to get more people involved, to stimulate debate, and hopefully to convince a few more people of the benefits of being part of the endocrinology community via the Society.'

Find out more about Nigel on the Society blog www.endocrinologyblog.org.

BECOME AN AMBASSADOR TODAY!

For more information and to apply visit www.endocrinology.org/membership/endocrine-ambassadors

Recognising and rewarding **EXCELLENCE**

The Society's medals are awarded to world-leading scientists and clinicians who have carried out landmark work during their careers: work that continues to inform research and best practice in endocrinology.

We congratulate our 2018 medallists, who will present their plenary lectures at the Society for Endocrinology BES conference on 19–21 November in Glasgow.



DALE MEDALLIST

Krish Chatterjee
Addenbrooke's Hospital,
Cambridge



INTERNATIONAL MEDALLIST

Ursula Kaiser
Brigham and Women's
Hospital, Boston, MA,
USA

JUBILEE MEDALLIST

Malcolm Parker
Imperial College
London



EUROPEAN MEDALLIST

Marie Christina Zennaro
Georges-Pompidou
European Hospital,
Paris, France



SOCIETY MEDALLIST

Stafford Lightman
University of Bristol



TRANSATLANTIC MEDALLIST

Joseph Takahashi
UT Southwestern
Medical Center,
Dallas, TX, USA

STARLING MEDALLIST

Leanne Hodson
University of Oxford



NOMINATE YOUR MEDAL WINNERS FOR 2019

Who do you think deserves recognition in 2019 for their contribution to endocrinology?

For details of the requirements for each medal and how to nominate visit www.endocrinology.org/grants-and-awards/prizes-and-awards/medals.

Nominations must be received by **2 July 2018**.

ENDOCRINE NURSE AWARD NOMINATIONS 2019

This is your opportunity to nominate an endocrine nurse who has demonstrated innovation and success in nurse-led initiatives that advance best practice and in research, education or patient care.

For more information and to make a nomination visit www.endocrinology.org/grants-and-awards/prizes-and-awards/endocrine-nurse-award.

Nominations must be received by **29 June 2018**.

10 things YOUR SOCIETY ACHIEVED IN 2017



www.endocrinology.org



You can read more at
www.endocrinologyblog.org/2017/12/21/10-things-your-society-achieved-in-2017

Early Career member? HERE'S WHY YOU SHOULD JOIN A COMMITTEE...



It's never too early to think about membership of one of the Society's committees. Early Career voices are valued; they

can bring a fresh perspective, highlight the issues that matter to clinicians and scientists in training, and provide views from the 'shop floor', whether that be the hospital or the laboratory. In return, committee membership can open up invaluable educational and career opportunities of which you might otherwise have been unaware.

I'm halfway through my term as one of the clinical trainee representatives on the Clinical Committee and on the Early Career Steering Group. I've thoroughly enjoyed working with the Society staff and getting to know my colleagues from across the UK. On a serious note, the Clinical Committee work has given me an insight into how policy changes come about, how guidelines are drawn up, and how services are designed and financed. On the fun side, I've had input into the programme for the S&E BES conference, and collaborated with colleagues from other organisations on events for trainees.

I'd urge anyone who is interested to consider joining a committee. The time commitment is not onerous (usually two or three meetings per year, plus email correspondence), and you'll undoubtedly find it a rewarding experience!

LOUISE HUNTER

Clinical Committee (Trainee Representative) & Early Career Steering Group

Committee membership has given me many career development opportunities, including lots of media experience and being part of the team redesigning the You and Your Hormones website.

CHANNA JAYASENA

Public Engagement Committee



Stand up, have a voice and challenge yourself. It gives you exposure and leadership opportunities.

ANNE MARLAND

Nurse Committee

Share opinions and ideas, and implement them in order to improve patient care.

JEREMY TOMLINSON

Council and Clinical Committee



See the ins and outs of the Society and understand why and how it evolves.

KIM JONAS

Science Committee

From January 2019 there will be vacancies on the following Society committees:

- Clinical
- Corporate Liaison
- Finance
- Nominations
- Nurse
- Programme
- Public Engagement
- Science

Visit www.endocrinology.org/about-us/governance/call-for-nominations to find out more about the work of each committee and to nominate before **29 June 2018**.

PPI: ITS IMPORTANCE IN THE DEVELOPMENT OF RESEARCH

WRITTEN BY ANNE MARLAND



Hopefully, everyone reading this article is familiar with PPI: not insurance which has potentially been mis-sold, but rather 'patient and public involvement'!

Humour aside, PPI is one of the most important factors influencing the development of research and, for most of us, affecting our successful delivery of metabolic and endocrine findings.

Good PPI improves the quality of research. Patients and the public can be involved in many ways, including helping to design research, making sure the research is relevant, advising on which research should be funded and reviewing project applications.

UNDERSTANDING INVOLVEMENT

INVOLVE is part of the National Institute for Health Research (NIHR). It defines public involvement in research as 'Research being carried out "with" or "by" members of the public rather than "to", "about" or "for" them. This includes, for example, working with research funders to prioritise research, offering advice as members of a project steering group, commenting on and developing research materials and undertaking interviews with research participants.'

INVOLVE uses the following terms to break down the activities.

Involvement

This is where members of the public are actively involved in research projects and in research organisations. Examples of public involvement include people taking part:

- as joint grant holders or co-applicants on a research project
- in identifying research priorities
- as members of a project advisory or steering group
- in commenting on and developing patient information leaflets or other research materials
- in undertaking interviews with research participants
- as user and/or carer researchers carrying out the research.

Participation

This is where people take part in a research study. Examples of participation are people joining in:

- as recruits to a clinical trial or other research study, to take part in the research
- to complete a questionnaire or participate in a focus group as part of a research study.

Engagement

In this case, information and knowledge about research are provided and disseminated. Examples of engagement are:

- science festivals open to the public with debates and discussions on research
- an open day at a research centre where members of the public are invited to find out about research
- raising awareness of research through media such as television, newspapers and social media
- disseminating the findings of a study to research participants, colleagues or members of the public.

HOW TO INVOLVE OTHERS IN YOUR RESEARCH

Hopefully most of you will be involved in some aspect of research – or maybe it's an area which you and colleagues in your department wish to explore. You have probably already considered why you want to involve the public or patients, and who you want to involve.

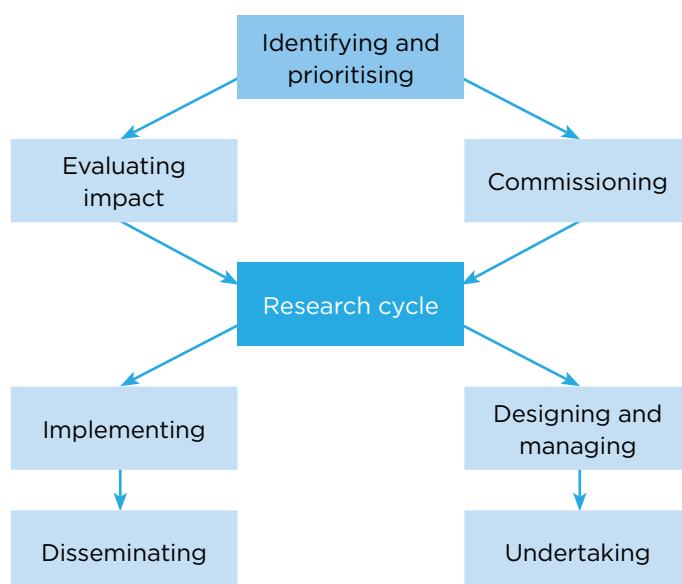
You now need to consider how these people are going to be involved in the different stages of the research cycle.

Nurses are perfectly positioned to play an important role in the process of involvement. We recognise and value the involvement of patients and the public in research. Nurses have excellent, advanced communication skills which demonstrate a desire to listen, understand and help with any question which may arise during an opportunity to discuss research with patients or the public. This establishes a therapeutic relationship with patients and the public with unconditional positive regard.

Within the context of the multidisciplinary research team, we offer a different perspective, where discussions with colleagues will help to alleviate 'jargon' and allow barriers to communication to be reviewed and addressed. Nurses act as the hub of communication, relaying and interpreting information between doctors, patients and carers. This ability provides the best possible outcomes for successful recruitment and involvement in research.

For many, the process will involve organising a meeting, for example, for project advisory groups, public events, reference groups or workshops. How you plan these meetings can make a huge difference to how people feel about the research and how much they are able and want to get involved in your work. Holding a meeting is only one of the ways to involve people, and you may decide that this is not the best approach for your research. There are many other ways of involving patients and public in research (see www.involve.nihr.ac.uk).

The research cycle. ©Anne Marland



LISA SHEPHERD

NURSE COMMITTEE CHAIR



WHAT TO CONSIDER WHEN ORGANISING MEETINGS

There are several factors that can aid your meeting's success:

- Explore opportunities for meeting patients or the public in their own environment, for example by attending a regular meeting of an organisation or group.
- Consider venues that are on neutral ground.
- Organise meetings at times and in places that make it easy for people to attend. Those who are working, have young children or are carers might need to meet outside office hours.
- Make sure that there is parking and public transport nearby.
- It may be better to plan for a mid-morning or early afternoon start to the meeting. This makes it easier for people if they have to travel some distance to attend or if they need additional time in the mornings because of their disability or health condition.
- Make sure meeting places, hotels and facilities are accessible to all those attending; for example, if you are inviting a wheelchair user to join your committee, meet in an accessible meeting room with parking nearby and fully accessible facilities.
- Where possible, visit the venue in person in advance of the meeting, and ask to be shown around to check its suitability and the access to all rooms, such as the dining area and disabled toilets. Don't rely on the venue telling you that it is accessible, as you might find that this is not the case or that the complex routes of access are not acceptable to the people needing access.

RUNNING THE MEETING

How the meeting is conducted is very important. Agree ground rules for how you will manage the meeting, so everybody has an equal opportunity to contribute. A Chair is necessary to keep balance and control. It is important that all group members, including members of the public, agree to these rules of mutual respect. Make sure that everybody has an equal voice in the group.

It is essential to encourage the use of clear language, and to explain jargon and acronyms. You should ask the Chair to check regularly that people understand the language used and the content of the meeting.

Frequent breaks and refreshments are important, as people might need to take medication or find sitting for long periods difficult. If it is possible to have a spare room, then allocate this as a quiet room for those who might need to take some time out of the meeting.

To allow people the opportunity to contribute in different ways, you might consider different ways to conducting meetings; for example, time in small group sessions, as well as meetings in a larger group. A mentor or buddy system can be useful to support the members of the public you are involving on an ongoing basis.

I hope reading this article will encourage you to involve PPI in your clinical setting, and that you can see how valuable it is to involve nurses, because of our skills related to all aspects of this approach. Our responsibility as nurses to the development and support of research is essential, and we can all make a difference.

ANNE MARLAND

PPI Nurse Representative for the NIHR Metabolic and Endocrine Specialty UK Group; Advanced Nurse Practitioner in Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford University Hospitals NHS Foundation Trust

Our first article of 2018 has been written by Anne Marland, from Oxford (page 26). Anne describes the fundamental and integral role that patient and public involvement (PPI) has in research: from conception, through involvement in the research and also in the dissemination of research outputs. Incorporating PPI strengthens the research process by understanding and representing the patients' perspective and experience. It is also valuable in the development of new services. Read Anne's suggestions to learn how you can involve PPI in your research.

If you are inspired to conduct some research, remember that the Society for Endocrinology Endocrine Nurse Grant (www.endocrinology.org/grants-and-awards/grants/endocrine-nurse-grant) is a great opportunity for nurses to improve research knowledge. Remember to embrace PPI and ensure that the perspective of the patient is at the heart of the research and that the study is important, meaningful, ethical and of high quality from conception to dissemination. Applications for the Endocrine Nurse Grant are currently welcomed, before the closing date of 23 May 2018.

I hope you have already registered for Endocrine Nurse Update 2018 on 16–17 April in Birmingham (www.endocrinology.org/events/endocrine-nurse-update). Our exciting programme reflects your feedback to incorporate more interactive sessions and networking opportunities.

Don't forget to nominate a nurse colleague for the Society for Endocrinology Endocrine Nurse Award 2019 (www.endocrinology.org/grants-and-awards/prizes-and-awards/endocrine-nurse-award). Nominees should have demonstrated innovative and successful nurse-led initiatives in endocrinology that have led to advanced best practice in research, education or patient care. The closing date is 29 June 2018.

I look forward to seeing you in April at Endocrine Nurse Update 2018 in Birmingham.

BEST WISHES

LISA SHEPHERD





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There are three grant rounds per year with deadlines on 31 March, 31 July and 30 November.

The Bioscientifica Trust was initiated by Bioscientifica Limited, a provider of publishing, event organization, and association management services to the global scholarly community, with the support of several of its clients. The Trust receives funds from Bioscientifica but is a wholly independent entity, governed by a Board of Trustees, and is in the process of registering as a charitable trust with the UK Charities Commission.

www.bioscientificatrust.org

UPDATE: SPECIALISED ENDOCRINOLOGY CRG

WRITTEN BY JOHN WASS



ENDOCRINOLOGIST MEMBERS OF CRG

Chair

John Wass

London

Simon Aylwin
Kevin Shotliff

Midlands & East

Neil Gittoes
Miles Levy

North

John Newell-Price
Peter Selby

South

Daniel Flanagan
Tristan Richardson

The Specialised Endocrinology Clinical Reference Group (CRG) had a very useful meeting at the Society for Endocrinology BES conference in Harrogate. CRG members Neil Gittoes and John Newell-Price, as well as Fausto Palazzo (Endocrine Surgeon, Imperial College London), talked about what we have been doing in the CRG to try and improve endocrine care up and down the country.

These processes have highlighted the importance of MDTs and their function in taking decisions in a multidisciplinary quorate manner before and after operation to predicate ongoing treatment through NHS England. In this respect, carefully developed and functional networks need to be in place.

‘These processes have highlighted the importance of MDTs and their function in taking decisions in a multidisciplinary quorate manner before and after operation to predicate ongoing treatment through NHS England.’

SURGICAL OUTCOMES

It is also important that endocrinologists know the outcome for highly specialised surgery. Cure rates according to the internationally accepted criteria should be known in terms of microadenomas and macroadenomas causing acromegaly and Cushing's. Likewise, outcomes in the field of thyroid and parathyroid surgery should be known; these can be accessed on the British Association of Endocrine and Thyroid Surgeons (BAETS) website at www.baets.org.uk. Thus hypocalcaemia rates after thyroid surgery and failed exploration rates after parathyroid surgery should be known by endocrinologists referring patients. They are quite variable.

‘It is really important that coding is attended to, particularly regarding surgical operations, and we are keen to have consultant input.’

THE DASHBOARD

John Newell-Price is currently masterminding the dashboard. Entering data into this is important from the point of view of specialised centres, and there will be reiterations in the next few months so that some new criteria are developed. Your input will be very gratefully received. Please contact your regional members of the CRG (listed above).

It is really important that coding is attended to, particularly regarding surgical operations, and we are keen to have consultant input. We are working with neurosurgeon Nick Phillips who is a member of the Stereotactic Radiosurgery CRG to optimise coding.

If you have any queries or comments, please get in touch at john.wass@nhs.net.

JOHN WASS

Professor of Endocrinology, University of Oxford
Chair, Specialised Endocrinology CRG

One important role for the CRG is to keep our community of endocrinologists properly informed and to provide the opportunity for feedback.

PEGVISOMANT AND PASIREOTIDE

Our several achievements include improving access to pegvisomant. This is undertaken through BlueTeq technology, and there are now 25 centres which can, subject to multidisciplinary team (MDT) approval, complete a form to access the drug. Responsibility for prescribing remains with the chair of the MDT. This is not arduous. A similar system is in place for pasireotide, but fewer centres have needed this and consequently around 10 have access to the BlueTeq technology.

‘One important role for the CRG is to keep our community of endocrinologists properly informed and to provide the opportunity for feedback.’

PARATHYROID HORMONE AND CINACALCET

There is on-going discussion within NHS England with regard to parathyroid hormone and cinacalcet, parathyroid hormone being used for the treatment of osteoporosis and cinacalcet for exploration-negative persistent hypercalcaemia in primary hyperparathyroidism. NHS England currently pays for these, and an IFR (individual funding request) needs to be made for parathyroid hormone. This is not particularly satisfactory, because of the prevalence of the need for these two drugs, and so the CRG is working to improve the situation.

Endocrine ACADEMY

16–18 April 2018

Hilton Birmingham Metropole, NEC, Birmingham, UK

Clinical UPDATE

16–18 April 2018

Clinical Update is a three-day residential course comprising lectures and interactive workshops. The small group workshops (50 delegates maximum) are targeted to specific topics on the curriculum.

Career DEVELOPMENT WORKSHOP

16–18 April 2018

Career Development Workshop is designed to meet the needs of basic scientists and clinician scientists, who are investing in building a career in academic research.

Endocrine NURSE UPDATE

16–17 April 2018

Endocrine Nurse Update is a two-day residential course for specialist endocrine nurses featuring interactive sessions, combined lectures, workshops and networking opportunities.

Registration is now open
and includes accommodation at the
Hilton Birmingham Metropole hotel.

Early bird deadline:
5 March 2018

Travel Grant application deadline:
14 March 2018 (noon)

Online registration deadline:
13 April 2018



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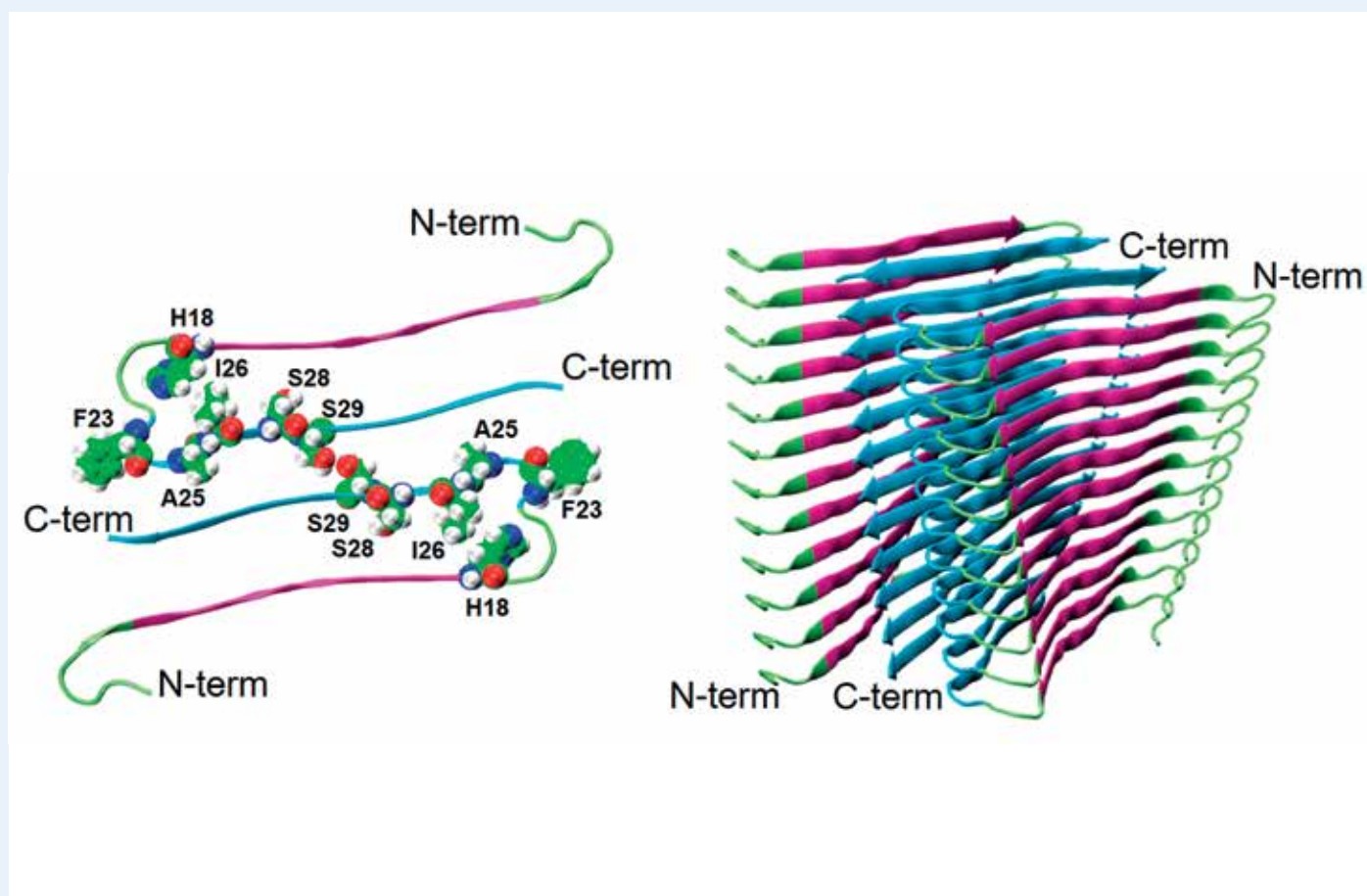
To view the programmes and register for any of the Endocrine
Academy events please visit www.endocrinology.org/events

Images in ENDOCRINOLOGY

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

COVER IMAGE FROM *JOURNAL OF MOLECULAR ENDOCRINOLOGY* JANUARY 2018

The image depicts two views of a model of the hIAPP (islet amyloid polypeptide) protofibril derived from crystallographic studies of peptide fragments (Wiltzius JJ *et al.* 2008 *Protein Science* 17 1467–1474). *Left:* A top-down view showing the horseshoe-shaped structure with the N- and C-termini (N-term, C-term) on the same face. There are no intra-peptide backbone hydrogen bonds in the structure; instead the backbone hydrogen bonding occurs between adjacent monomers in one of the stacks. *Right:* The two stacks are aligned so that two molecules lie antiparallel in the same plane and interact via their side chains.. From Raleigh *et al.* 2017 *Journal of Molecular Endocrinology* 59 R121–R140. Credit: X Zhang (Stony Brook University, NY, USA).



Enter our Cover Art Competition

for *Journal of Endocrinology*, *Journal of Molecular Endocrinology* and *Endocrine-Related Cancer*.

See Instructions for Authors on the journal homepages for more information (<http://joe.endocrinology-journals.org>, <http://jme.endocrinology-journals.org>, <http://erc.endocrinology-journals.org>).

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if testosterone deficiency has not been demonstrated and if other aetiologies have not been excluded. Not indicated for treatment of male sterility or impotence. Monitor testosterone at regular intervals. Adjust dose to maintain eugonadal testosterone level. Experience in patients over 65 years is limited; account for lower serum testosterone with increasing age. Pre-examine all patients to exclude a risk of pre-existing prostatic cancer. Perform regular monitoring of blood and prostate. Androgens may accelerate the development of subclinical prostatic cancer and benign prostatic hyperplasia. Use with caution in thrombophilia due to risk of thrombosis. Monitor haemoglobin, and haematocrit, liver function tests and lipid profile during long-term use. Oedema with/without congestive heart failure may be a severe complication in patients with pre-existing severe cardiac, renal, or hepatic insufficiency or ischaemic heart disease. Discontinue immediately if such complications occur. Use with caution in hypertension, epilepsy, migraine and sleep apnoea as these conditions may be aggravated. Care should be taken with skeletal metastases due to risk

of hypercalcaemia/hypercalcaemia. Androgen treatment may result in improved insulin sensitivity. Inform the patient about the risk of testosterone transfer and give safety instructions. Health professionals/carers should use disposable gloves resistant to alcohols. **Side-effects:** Very common: Application site reactions (including paresthesia, xerosis, pruritis, rash or erythema). Common: Increased haemoglobin, red blood cell count, and haematocrit. Increased male pattern hair distribution. Hypertension, gynaecomastia, peripheral oedema, and increased PSA. May cause irritation and dry skin. Prescribers should consult the summary of product characteristics for further details of side effects. **Legal Category:** POM. **Further information is available from the Marketing Authorisation Holder:** Kyowa Kirin Ltd, Galahack Business Park, Galahack, TD1 1QH, UK. **Date of Prescribing Information:** March 2017.

For the United Kingdom: Pack Size and Price: Pack contains one 60 g metered-dose canister. Price £28.67. **Marketing Authorisation Number:** PL14508/0025.

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References: 1. Tostran[®] Summary of Product Characteristics. 2. eMMS January 2018. 3. Morgentaler A, et al. Steady-state pharmacokinetics. SMSNA Annual meeting 2011.

Date of preparation: January 2018. Job code: UK/M015/0507

KYOWA KIRIN

