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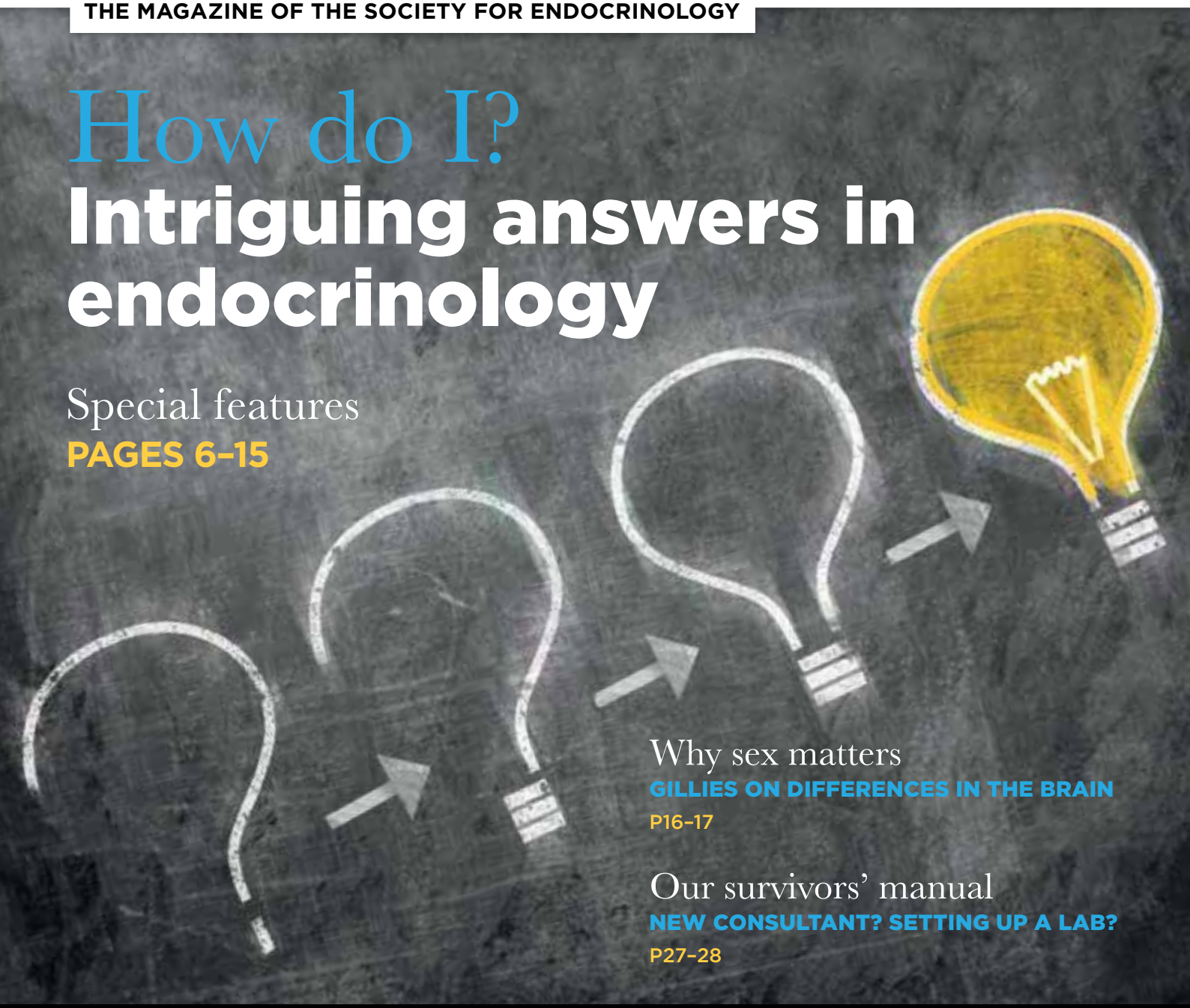
THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY



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A word from THE EDITOR...

Having a really good idea is not something that happens very often, at least not to me. I know I make a lot of decisions each week, and most of the time I have an idea of what to do, but increasingly that relies on process and experience.

I'm thinking about those REALLY good ideas that apparently reveal themselves to an individual in a moment of pure clarity, and make those around them green with 'why didn't I think of that?' envy. The zip, cat's eyes in the road, pivoted scissors, Lego … all genius answers to the questions of how to make clothes fit, see where to drive, hold and cut material with one hand and build a bespoke model rocket that doesn't need glue.

In the retelling, these ideas are sold as having arrived fully formed, out of nothing, but I think the maxim that genius is 1% inspiration, 99% perspiration still mostly holds true. The original light bulb man Thomas Edison had a whole team of people trying out thousands of different filaments before they settled on a winner, and it's hard to get past that rule of 10,000 hours of time needed to get good at something.

So, one way to overcome a problem is to be born with a high degree of innate talent, start perspiring and wait. However, a less sweaty and shorter way to get a solution may be to ask someone who has already conquered it and use their idea. In this issue, we go from macro to micro, from sick horses to extracellular vesicles, to tap into the knowledge of people from all across the patch.

Fran Ebling and Jo Lewis give a biological basis to winter survival strategies, while Kim Jonas shows you how to use super-resolution microscopy to resolve how proteins interact. Jeremy Tomlinson gives sage advice on how to think about the HPA axis in the critically ill, and Phil Ambery and Lutz Jermutus walk us through the tricky task of shepherding a drug into clinical practice.

Tips from Matthew Simmonds and Dominic Cavlan should steady faint hearts moving up the career ladder to more senior positions. Finally, in the pursuit of understanding how we think and what shapes our thought processes and ideas, Glenda Gillies' article serves as an encouraging reminder that all the really interesting aspects of human behaviour are hugely influenced by hormones. Which is, of course, another reason to do what we do.

BEST WISHES

TONY COLL

Society for Endocrinology
22 Apex Court, Woodlands,
Bradley Stoke, Bristol BS32 4JT, UK
Tel: **01454 642200**
Email: **info@endocrinology.org**
Web: **www.endocrinology.org**
Company Limited by Guarantee
Registered in England No. 349408
Registered Office as above
Registered Charity No. 266813

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Please contact **Jennie Evans**
endocrinologist@endocrinology.org

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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 2017 issue: **20 March 2017**.

Deadline for news items for the Autumn 2017 issue: **10 July 2017**.

Front cover image ©SHUTTERSTOCK

UPDATES AT *THE ENDOCRINOLOGIST*

We're delighted to welcome two members to the Editorial Board of *The Endocrinologist*: Dr Lisa Nicholas (Cambridge) and Dr Helen Simpson (London). Our grateful thanks go to retiring Board members Rosemary Bland and Dominic Cavlan for all their hard work and input over the past 2 years.

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 **endocrinologist@endocrinology.org**.

Lisa Nicholas

Helen Simpson

COMMITTEE VACANCIES

Would you like to join a Society committee and make a difference? We will have a number of vacancies at the end of this year on the Society's Clinical, Finance, Nurse, Programme, Public Engagement and Science Committees as well as on the Corporate Liaison Board and Early Career Steering Group. You can find more information at **www.endocrinology.org/about-us/governance**. The deadline for nominations is 30 June. Learn more about what it's like to be on a Society committee and why you should apply on pages 22–23.

EARLY CAREER PRIZE LECTURES

CALL FOR ABSTRACTS!

Have your work recognised more widely across the endocrine community with the help of these prize lectures, intended to support Clinicians-in-Training and Scientists-in-Training. We are now inviting abstracts for one basic science and one clinical lecture. The winners will each receive an honorarium of £750 and present a 20-minute lecture at the Society for Endocrinology BES conference in November 2017. Full details are available at **http://bit.ly/SfEECPL**. The deadline for entries is 10 April 2017.

ENDOCRINOLOGY IN RCP SPOTLIGHT

The Royal College of Physicians featured endocrinology and diabetes in their January Specialty Spotlight. Highlighting that it is 'one of the most challenging, rewarding and wide-ranging of the medical specialties', they include a range of resources for trainees who are considering a career in endocrinology and diabetes.

In a video interview, Oxford University's John Wass (Professor of Endocrinology) and Ioannis Spiliotis (Clinical Research Fellow and Honorary Specialty Registrar in Diabetes and Endocrinology) discuss what's involved in working in endocrinology and diabetes and give advice on how to enter the discipline.

You can find out more at **http://bit.ly/RCPEndo**.

OFFICER VACANCIES

The Society's General Secretary Karen Chapman and Programme Secretary Simon Pearce will complete their terms of office at the 2018 AGM. We are therefore seeking their replacements to become officers-elect at the 2017 AGM, before starting their 3-year terms in full office at the 2018 AGM. You can find job descriptions and the responsibilities of trustees at **www.endocrinology.org/about-us/governance**.

Council has nominated Professor Eleanor Davies (Glasgow) for the position of General Secretary and Professor Duncan Bassett (London) for the position of Programme Secretary. If any member wishes to make further nominations by 24 March 2017, please contact **members@endocrinology.org** for a nomination form.

WITH REGRET

We are sorry to announce the deaths of Peter Moult, formally of the Whittington Hospital, and Roger Ekins, formally of University College London. Full obituaries will appear in the next issue of *The Endocrinologist*.

SOCIETY CALENDAR

20–22 March 2017
CLINICAL UPDATE
Birmingham

20–21 March 2017
ENDOCRINE NURSE UPDATE
Birmingham

6–8 November 2017
SfE BES CONFERENCE
Harrogate

www.endocrinology.org/events for full details

SOCIETY SUPPORTED EVENTS

27 August–1 September 2017
NUCLEAR RECEPTORS & EPIGENETIC CHANGES IN DISEASE & AGEING
Spetses, Greece

29 August–2 September 2017
22ND WORLD CONGRESS OF THE INTERNATIONAL FEDERATION FOR THE SURGERY OF OBESITY & METABOLIC DISORDERS
London

GRANT AND PRIZE DEADLINES

11 March 2017
SUMMER STUDENTSHIPS

15 March 2017
TRAVEL GRANTS

31 March 2017
PUBLIC ENGAGEMENT GRANTS

10 April 2017
EARLY CAREER PRIZE LECTURES

15 April 2017
REGIONAL CLINICAL CASES MEETING GRANTS

17 April 2017
PRACTICAL SKILLS GRANTS

8 May–31 July 2017
SfE BES REGISTRATION GRANTS

27 May 2017
EARLY CAREER GRANTS

27 May 2017
EQUIPMENT GRANTS

31 May 2017
THEMED SCIENTIFIC MEETING GRANT

14 June–12 July 2017
UNDERGRADUATE ACHIEVEMENT AWARDS

16 June 2017
MEDAL NOMINATIONS

16 June 2017
ENDOCRINE NURSE AWARD

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

HOT TOPICS

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

Diet-dependent effects on gut bacteria composition

The key role played by gut bacteria in mediating a wide range of effects on host physiology is now starting to be understood. In this study, Johnson *et al.* examined whether the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) can influence the gut bacteria and, if so, whether these effects are diet-dependent.

Using 11β-HSD1-deficient mice, they found that a lack of 11β-HSD1 had a significant effect on the abundance of certain families of gut bacteria compared with controls, and that these results were dependent on diet. Alterations were observed in the relative abundance of *Prevotellaceae* when mice were fed a standard chow diet, with the relative abundance of *Bacteroidaceae* increasing when they were fed a Western diet (high fat, cholesterol-enriched).

Although the mechanisms that underlie these findings are currently unclear, they imply that genetic effects on host–microbiome interactions can depend on diet, and that diet may be influential in some of the metabolic and inflammatory phenotypes observed in 11β-HSD1 deficiency.

Read the full article in *Journal of Endocrinology* **232** 273–282

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Understanding 11β-HSD1's role in the myocardium

Glucocorticoid metabolism is exquisitely controlled by isoforms of the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD). Although the regulation of glucocorticoid activity by 11β-HSD type 1 (11β-HSD1) has been characterised in several tissues, understanding of the functional role of glucocorticoid metabolism by 11β-HSD1 in the heart has remained elusive.

In this review, Gray *et al.* explore the evidence for the functional and physiological roles of glucocorticoid metabolism in the heart, including postnatal growth of the myocardium and development of coronary heart disease, and the response to myocardial infarction-induced injury.

Read the full article in *Journal of Molecular Endocrinology* **58** R1–R13

ENDOCRINE-RELATED CANCER

Twists and challenges in resistance to hormonal therapies for cancer

December's issue of *Endocrine-Related Cancer* features an interesting series of thematic reviews centred on hormone-mediated cancers, focusing on prostate cancer and breast cancer.

The six reviews present a tour de force of the key concepts, novel aspects and current therapeutic challenges and emerging treatment options for these two prominent cancers. Emerging therapeutic strategies to overcome resistance to hormonal therapies and advances in patient-derived xenografts to better model solid tumours are presented.

This interesting and stimulating collection of articles provides much food for thought: a 'must read'.

Read the full section in *Endocrine-Related Cancer* **23** E9–E12, T179–T270

ENDOCRINE HIGHLIGHTS

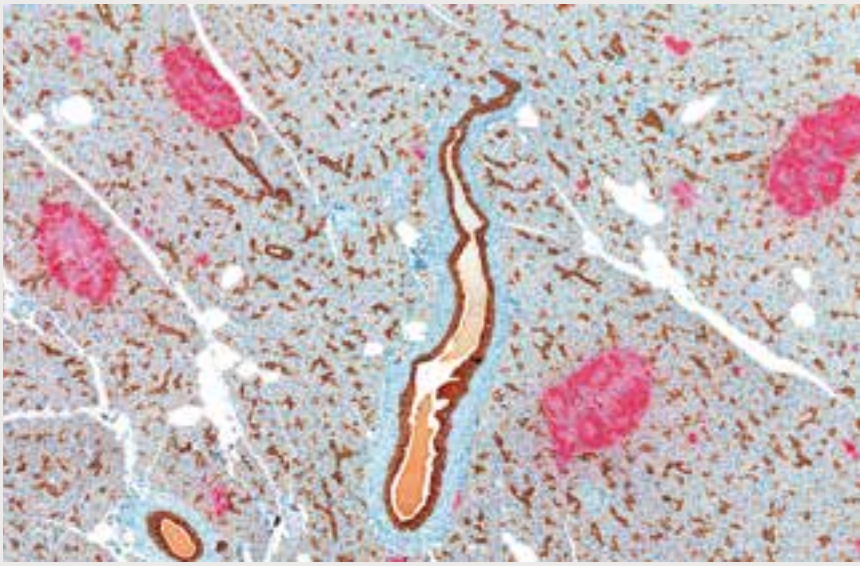
A summary of papers from around the endocrine community that have got you talking.

PLIN2 and endoplasmic reticulum stress resolution in pancreatic β-cells

A common feature of type 2 diabetes is increased plasma levels of non-esterified fatty acids, which are usually stored in cells as triglycerides and lipid droplets. Perilipin 2 (PLIN2) is a lipid droplet protein that is constitutively expressed in all cells. Its expression has been shown to be increased in pancreatic β-cells exposed to fatty acids. It is also known that prolonged exposure to fatty acids leads to endoplasmic reticulum (ER) stress-induced apoptosis in β-cells.

Chen *et al.* therefore sought to determine whether PLIN2 plays a role in modulating ER stress in β-cells of Akita mice, which display severe ER stress and diabetes. They found that PLIN2 regulates ER stress in the β-cells of these mice and that loss of PLIN2 confers protection from diabetes by improving glycaemia and partially preserving β-cell mass by alleviating ER stress-induced apoptosis. This was achieved through modulation of autophagic flux, resulting in increased basal autophagy in β-cells of Akita mice. This study has, therefore, shed light on a previously under-appreciated role for PLIN2 in pancreatic β-cells.

Read the full article in *Scientific Reports* **7** 40855



Pancreas showing multiple islets of Langerhans containing β-cells stained immunohistochemically for insulin (red) with ducts stained for cytokeratin (brown). ©Shutterstock

Hot Topics is written by Ben Challis, Tony Coll, Jennie Evans, Lisa Nicholas, Amir Sam and Helen Simpson.

CLINICAL ENDOCRINOLOGY

Effect of GH deficiency on social development

While we know that hypopituitarism diagnosed at an early age has the potential to influence growth and somatic development, we understand relatively little about how this condition affects other facets of development.

Mitra and colleagues analysed information from the KIMS database (Pfizer International Metabolic Database) on the long term safety and clinical outcomes of growth hormone (GH) replacement in GH-deficient adults. Their aim was to examine how social, education and vocational outcomes were affected by onset of GH deficiency in childhood, adolescence and young adulthood, compared with adult-onset controls.

They found patients diagnosed during childhood (<16 years) and in young adulthood (16– 25 years) were 4.5–8 times more likely to live at home with their parents. They were also significantly less likely to live with a partner or to have children. No significant differences were found in educational or vocational attainments between the groups.

The authors conclude that the identification of differences in social attainment should be fed into the delivery of endocrine care in both paediatric and adult services.

Read the full article in *Clinical Endocrinology* doi: 10.1111/cen.13291

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Diagnosing acromegaly caused by ectopic GHRH from bronchial carcinoid

Acromegaly caused by ectopic growth hormone-releasing hormone (GHRH) secretion from a bronchial carcinoid tumour is very rare, accounting for fewer than 1% of cases of the disease. This case study highlights how difficult it can be to make the diagnosis.

Kyriakakis and colleagues clearly describe the biochemical, radiological and histopathological features. They emphasise that pituitary hyperplasia can be difficult to differentiate from an adenoma. This demonstrates the importance of reviewing the histology in a pituitary multidisciplinary team and of access to an experienced pituitary histopathologist. This case also shows the benefit of reviewing complex cases years after diagnosis, when new techniques are available.

Here, GHRH staining confirmed the diagnosis of ectopic GHRH secretion from the bronchial carcinoid tumour. A complete diagnosis could have implications for follow up and disease surveillance. A negative *MEN1* gene test is particularly noteworthy, as this would have implications for follow up and further testing of family members.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* EDM160104

ENDOCRINE CONNECTIONS

Metabolic and endocrine care during transition

In this review, Hokken-Koelega and coworkers beautifully highlight the challenges of managing the care of patients when they move between paediatric and adult services. It describes the many factors that need to be considered, from differing medical diagnoses to coming to terms with issues such as loss of fertility during the teenage years, which can be difficult enough without also having to cope with a long term health condition.

The authors describe different models of care, but emphasise that one size does not fit all. They highlight the importance of developing multidisciplinary teams, sharing information between paediatric and adult services and developing trust and relationships with new healthcare providers, which are important for both patients and their parents. Discussion also touches on issues such as sexual health, contraception and drug use and misuse, subjects which are often avoided by paediatric and adult physicians alike.

As well as giving a good overview of the challenges involved in transitioning between paediatric and adult services, the authors provide food for thought when considering how we deliver our services.

Read the full article in *Endocrine Connections* **5** R44–R54

^{177}Lu-Dotatate in advanced midgut NETs

Neuroendocrine tumours (NETs) of the midgut are rare, often indolent tumours. However, many patients are diagnosed with metastatic incurable disease at initial presentation. Due to their anti-secretory and anti-proliferative actions, somatostatin analogues are used as first-line systemic therapy. To date, cytotix chemotherapy, radiotherapy and newer biological agents have not been found to be effective in managing metastatic disease.

Recently, Strosberg and colleagues reported results from the Neuroendocrine Tumours Therapy (NETTER-1) Study, a phase 3 randomised controlled trial (RCT) evaluating the efficacy and safety of ^{177}Lu-Dotatate compared with high dose octreotide LAR in advanced progressive somatostatin receptor-positive midgut NETs.

^{177}Lu-Dotatate treatment resulted in a significantly longer progression-free survival rate and higher response rate. In a planned interim analysis, overall survival also increased following ^{177}Lu-Dotatate therapy. However, clinically significant haematological toxicity occurred in 10% of those treated.

This is the first RCT to demonstrate ^{177}Lu-Dotatate as an efficacious second-line treatment in advanced and progressive midgut NETs. This further supports provision of ^{177}Lu-Dotatate to such patients in England, in line with other countries, and guidance such as that from the European Neuroendocrine Tumour Society.

Read the full article in *New England Journal of Medicine* **376** 125–135

Low thyroid hormone may alter fetal pancreas development

Adequate thyroid hormone during pregnancy is needed to ensure the normal growth and development of the fetus, and for long term control of carbohydrate metabolism throughout life.

Harris and coworkers used a sheep animal model to examine whether thyroid hormone affects β-cell proliferation in fetal pancreatic islets. Through a series of experiments, they found that hypothyroidism in the fetus has a number of effects on the pancreatic islets. In fetuses whose thyroid gland had been removed, they observed an asymmetric pattern of organ growth, pancreatic β-cell hyperplasia and elevated plasma insulin and leptin levels. When the pancreatic islets were studied *in vitro*, β-cell proliferation was inhibited by thyroid hormone in a dose-dependent manner, while exposure to insulin and leptin resulted in β-cell proliferation.

This study shows the importance of physiological exposure to appropriate levels of thyroid hormone, insulin and leptin *in utero* and hints that this may have possible consequences for carbohydrate metabolism later in life.

Read the full article in *Journal of Physiology* doi:10.1113/JP273555


Credit Wolfgang Goymann

Ghrelin control of migratory behaviour in birds

Every year, billions of birds make the long journey from sub-Saharan Africa to Europe and back. The majority of migratory species that undertake this gruelling journey need to make 'pit-stops' on the way, in order to replenish their fuel reserves. But what signals tell the birds when they have eaten enough to allow them to move on again?

Goymann *et al.* studied wild garden warblers (*Sylvia borin*) at a well known stop-over site for the species on the island of Ponza in Italy. They found that birds with high fat scores (i.e. those that were well nourished) had higher acylated ghrelin concentrations compared with those with lower fat scores. Additionally, when the birds were given an injection of unacylated ghrelin, their food intake decreased, while their migratory restlessness increased.

This study provides the first evidence for a role for the appetite-regulating hormone ghrelin in the control of migratory behaviour, linking how ecologically dependent factors such as condition can affect the timing of migration.

Read the full article in *Proceedings of the National Academy of Sciences of the USA* doi:10.1073/pnas.1619565114

HOW DO I ... APPLY SUPER-RESOLUTION FLUORESCENT MICROSCOPY TO ENDOCRINOLOGY?

WRITTEN BY KIM JONAS

Credit: K Jonas

As our quest for understanding the molecular mechanisms underpinning endocrine pathways and pathologies intensifies, the requirement for visualising cellular processes in high definition is ever-pressing. As such, the last 10–15 years have witnessed a technological explosion in the field of microscopy, resulting in the advent of super-resolution imaging.

Indeed, the importance of this fast-moving field was recently recognised by the Nobel Committee for Chemistry, as three pioneers of super-resolution microscopy – Eric Betzig, William Moerner and Stefan Hell – were awarded the 2014 prize for localisation microscopy and stimulated emission depletion (STED) respectively.

THE SIGNIFICANCE OF SUPER-RESOLUTION IMAGING

'But what exactly is super-resolution imaging?' I hear you ask. The exciting development it brings is the ability to break the diffraction limit. Most of the commonly used microscopy techniques, such as confocal and widefield microscopy, have a maximum (and often theoretical) resolution of 200nm. Super-resolution imaging provides enhancements in resolution of between 2- and 20-fold, depending on the sample used and technique employed.

So, for the first time, we can resolve true single molecules which, for those interested in receptor-mediated processes, or protein–protein and protein–DNA interactions, provides the possibility of imaging these processes in high definition.

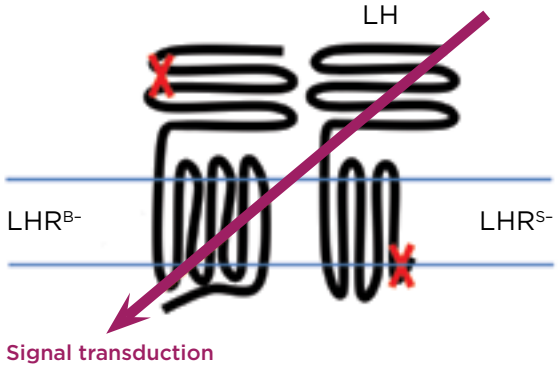
QUESTIONS WITH G PROTEIN-COUPLED RECEPTORS

For my own research, super-resolution imaging has been transformative. A long-debated question in the G protein-coupled receptor (GPCR) field is the functional significance of GPCR di/oligomerisation, particularly for family A receptors. Our previous studies had shown that the luteinising hormone receptor (LHR), a receptor essential for reproduction, can act via di/oligomerisation *in vivo*, using a functional complementation approach. This was the first study to present conclusive evidence for the physiological relevance of family A receptor di/oligomerisation.

However, despite this leap in understanding, we still lacked knowledge about the cell surface landscape of the LHR. We therefore wanted to know whether the LHR formed dimers or oligomers. Additionally, if oligomers were formed, what types of oligomeric forms could be observed and were they ligand-regulated?

To answer these questions, we went back to an *in vitro* model, using HEK293 cells stably expressing either the LHR or the functional complementation LHR mutants employed in our *in vivo* study: a ligand-binding deficient LHR (LHR^{B-}) and a signalling deficient LHR (LHR^{S-}) which, when co-expressed, recapitulated LHR function via di/oligomerisation (Figure 1).

Figure 1. Schematic representation of LHR functional complementation. Co-expression of ligand-binding deficient LHR (LHR^{B-}) and signalling deficient LHR (LHR^{S-}) can restore LHR function via di/oligomerisation.
Credit: K Jonas



'For the first time, we can resolve true single molecules which, for those interested in receptor-mediated processes, or protein–protein and protein–DNA interactions, provides the possibility of imaging these processes in high definition.'

ANSWERS FROM SUPER-RESOLUTION IMAGING

To image the cell surface landscape of the LHR, we employed the super-resolution imaging technique of photoactivatable localisation microscopy (PALM). PALM was used as it afforded a resolution of <10nm, meaning that we could image individual LHR molecules at the cell surface and thus identify the monomer/dimer/oligomer populations of LHRs.

PALM is based upon the use of photoactivatable fluorophores, which remain in the dark state until activated by ultraviolet light. The fluorophores are activated in a stochastic fashion, emitting fluorescence in the fluorophore-defined wavelength, and are subsequently photo-bleached into the dark state (Figure 2). The important aspect for identifying single molecules (and the premise of the technique) is the stochastic nature by which fluorophores are activated, allowing spatially separate detection of activated fluorophores, and thus single molecule detection. Samples are subjected to repeated cycles of activation and photo-bleaching to ensure all fluorophores are imaged.

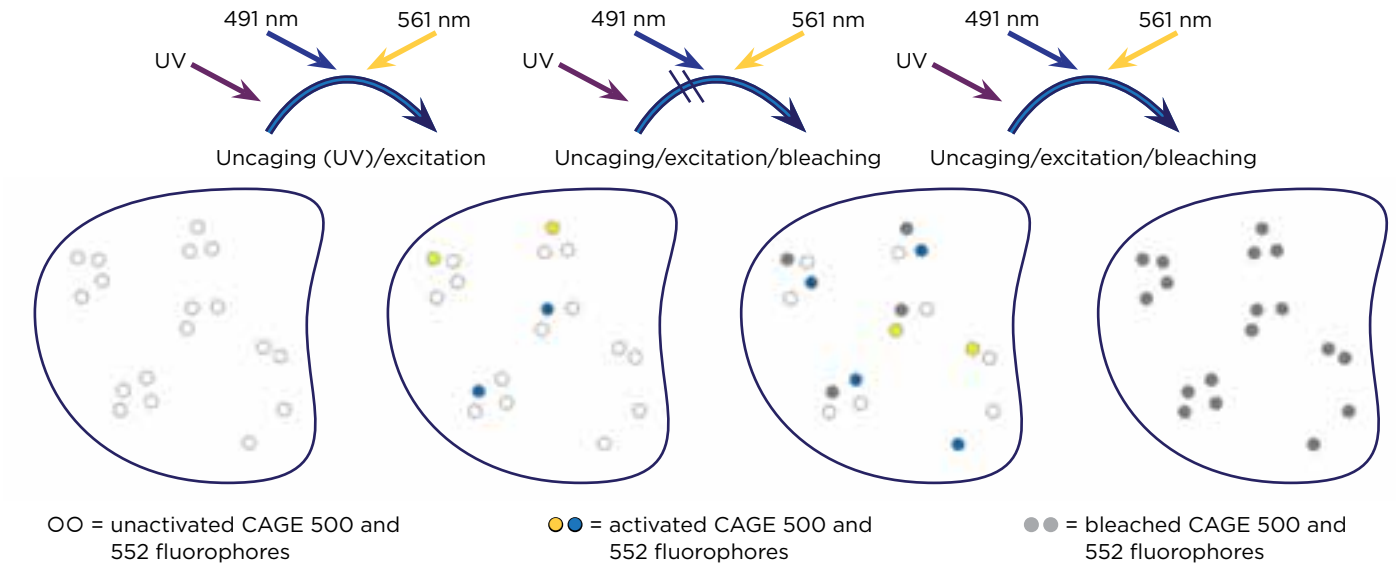
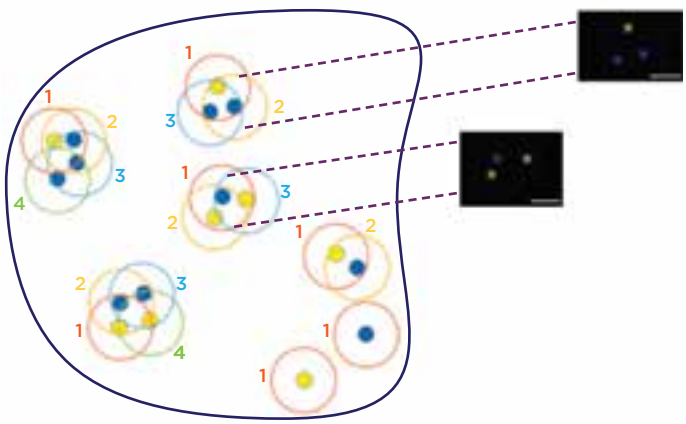


Figure 2. The principles of PALM. Fluorophores are activated by UV, and detected and photo-bleached by fluorophore-defined laser wavelengths. Multiple cycles of activation, detection and bleaching are carried out, until all fluorophores are bleached. Adapted from *Journal of Biological Chemistry* **290** 3875–3892

The fluorophores we employed were CAGE dyes – CAGE 500 and 552 – which are brighter than most photoactivatable proteins available. They could also be directly conjugated with primary antibodies to the small peptide-tagged LHRs at a 1:1 dye:antibody ratio, allowing for direct quantification of LHR protomers.

Due to the high laser power and repeated cycles of activation and photo-bleaching that are required to image samples, PALM was conducted on fixed cells using a custom-adapted Inverted Axiovert 200 wide-field fluorescent microscope (Zeiss, Germany) fitted with a commercial TIRF (total internal reflection fluorescence) condenser and a polychrome light source.

Figure 3. Post-acquisition analysis of PALM data. Nearest neighbourhood analysis shows the detection of monomers, dimers, trimers, tetramers and resulting resolved LHR molecules. Scale bar=50nm. Adapted from *Methods in Cell Biology* **132** 55–72



INTERPRETING THE DATA

Once imaging has been carried out, a large (and time consuming!) part of localisation microscopy is the post-acquisition data analysis to 'localise' the molecules imaged. To resolve the *x* and *y* co-ordinates of the LHRs, we used the free ImageJ plugin, QuickPALM. This software identified individual LHRs from image files, using a set of in-built stringency filters to ensure the integrity of the data generated.

Once the co-ordinates were obtained, we interrogated our study questions. To identify LHR participating in dimers and oligomers, we employed a mathematical model adapted from the Getis–Franklin nearest neighbourhood approach (Figure 3).

Our analysis revealed that approximately 40% of LHRs were in di/oligomers in both the wild type LHR and functional complementation LHR^{B-}/LHR^{S-}. Interestingly, LHR^{B-}/LHR^{S-} favoured the formation of oligomers. No ligand-dependent changes in the number of di/oligomers were observed. However, modulating the ratio of LHR^{B-}:LHR^{S-} within lower order oligomers regulated the magnitude of G protein-dependent signal output.

Our studies show how super-resolution imaging can be used to provide such levels of unprecedented molecular detail, revealing how receptors within an oligomer can fine-tune signal responses.

KIM JONAS
Lecturer in Reproductive Physiology, St George's University of London

FURTHER READING

1. Jonas KC *et al.* 2016 *Methods in Cell Biology* **132** 55–72.
2. Jonas KC *et al.* 2015 *Journal of Biological Chemistry* **290** 3875–3892.

HOW DO I ... MEASURE EXTRACELLULAR VESICLES IN MY SAMPLES?

WRITTEN BY CHARLOTTE LAWSON

Extracellular vesicles (EV) are sub-micron, lipid-encased particles that have been found in all bodily fluids so far tested, including plasma, urine, milk, tears, sweat and semen. They have also been identified in the plant kingdom and in micro-organisms.

The vesicles typically carry a cargo which can include genetic material such as mRNA, genomic DNA and microRNA (miRNA). They may also carry proteins such as growth factors, enzymes and cytokines. Thus, they can be considered as intercellular transport vehicles, with the capacity to influence the behaviour of distant cell types within the body, as well as being important for the transfer of information between individual organisms of the same or separate species.

Until relatively recently, all classes of EV were considered cell debris and not worthy of further study. However, there is now a growing body of evidence to suggest that they have potential as biomarkers or as mediators of disease in a range of different conditions including cardiometabolic disease and diabetes.[1]

CLASSES OF EXTRACELLULAR VESICLES

Typically, EV are divided into three main populations according to their diameters: exosomes at 50–100nm, microvesicles (MV; microparticles) at 100nm–1µm, and apoptotic bodies at usually greater than 1µm.

Exosomes are produced via an endosomal pathway which involves formation of multivesicular bodies that are trafficked to the plasma membrane, where they fuse to release their exosomal contents. In contrast, both MV and apoptotic bodies are formed by budding or blebbing of the cell membrane to pinch off new vesicles, in a calcium-dependent process (Figure).

This article will concentrate on the measurement and isolation of exosomes and MV.

SEPARATION METHODS

Size ranges of different EVs may overlap, and the markers which are displayed on the outer leaflet of the surrounding membrane may be common to both exosomes and MV. Thus, most isolation methods do not guarantee a pure population of vesicles. With this in mind, and based on the most common protocols involving sequential ultracentrifugation steps, some researchers now refer to each population by the speed at which it is pelleted, rather than referring to exosomes or microvesicles.

There are guidelines available for the collection of blood in particular,[2] and several protocols have been published for the sequential isolation of different populations via ultracentrifugation.

In the first step, bodily fluid or culture medium is centrifuged at low speed (1,500–3,000×g (times gravity)) to remove cellular material and debris. The supernatant from this step can then be further centrifuged at 10,000–17,000×g to pellet MV, with a final centrifugation at 100,000×g to pellet exosomes. In addition to exosomes, this population is likely to contain small MV and possibly some lipoproteins. Density gradient ultracentrifugation may be further employed for a purer exosome population.[3]

In addition, commercially available kits utilise size exclusion chromatography and magnetic separation based on CD9 or CD63, cell surface markers which are exposed on exosomes but not thought to be expressed on MV. Exosomes are directly precipitated from plasma or culture supernatant using these approaches.

However, there is no clear consensus as to the efficacy of these methods in the published literature. For these reasons, it is imperative to characterise the population of interest as fully as possible.

CHARACTERISING EXTRACELLULAR VESICLES

A selection of methods have been utilised for characterisation of EV. Electron microscopy (EM) is considered the gold standard, as it is can give accurate information about the sizes of all classes of vesicle. However, as it is not a quantitative technique and requires specialised expertise and equipment, EM may be of limited appeal. Several other non-optical methods have also been utilised but are limited by the same constraints.

Schematic representation of the mechanisms of formation of microvesicles, exosomes and apoptotic bodies.
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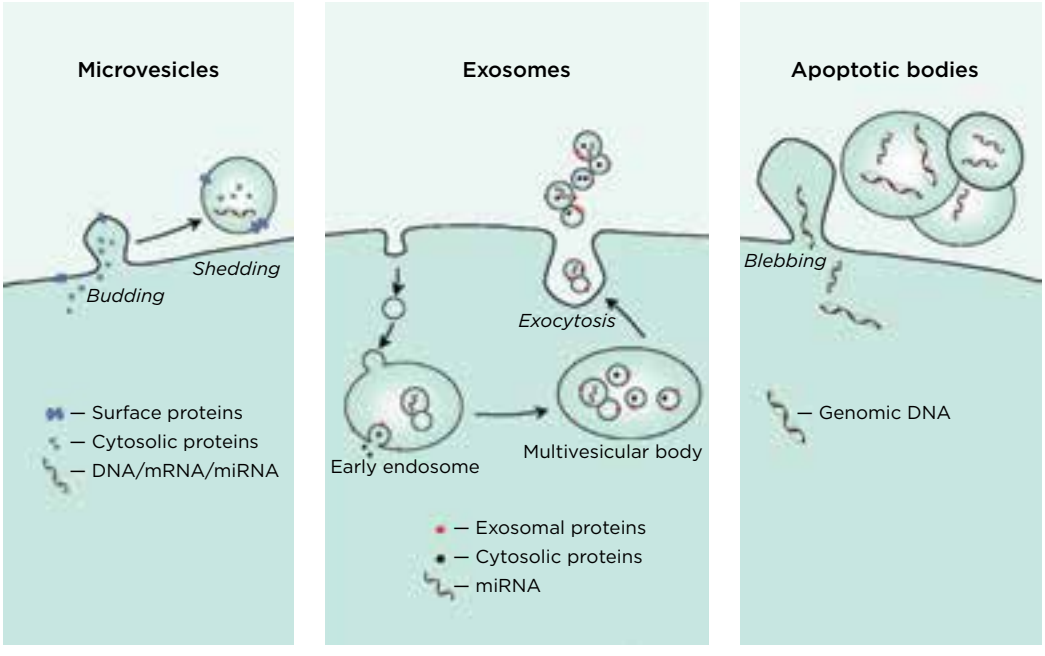


HOW DO I ... PREPARE FOR WINTER?

WRITTEN BY FRANCIS EBLING & JO LEWIS

After 30+ years as an academic researcher, Francis Ebling suggests that the best advice for surviving winter is to use the Christmas break or February half term to fly south for sun and warmth: 'Mauritius and St Lucia are particularly agreeable but I'm looking forward to the day when I head down under to watch Joe Root lead a side to retain the Ashes!' In contrast, as an early career researcher and impoverished parent, Jo Lewis' advice adopts the more economical strategy of a thick sweater and warm coat. But for guidance of a more endocrinological nature, read on...

Francis Ebling (left) and Jo Lewis (right) with Russell Foster (centre), whose lab has identified the retinal mechanisms by which mammals detect changes in day length (see *The Endocrinologist* issue 122, page 6).

By the time you're reading this, it will be too late to take action for winter 2016/17. In fact, most of our fellow species that are indigenous to Britain will be preparing for spring! Preparations for winter started soon after the summer solstice, as the gradual shortening of day lengths signalled that breeding should finish, fat stores be replenished, winter coat be grown, and a winter survival strategy enacted. For many of our avian friends, the winter plan is to head south of the equator to warmer climes where the day lengths are longer and food supply plentiful.

Our terrestrial counterparts obviously don't have the option of a winter migration, but delving into a hibernaculum is perhaps an equally agreeable strategy. Actually, very few mammalian species indigenous to Britain truly hibernate, just a few species of bats and the dormouse – and when did you last see a dormouse, other than in the local panto production of 'Alice in Wonderland', played by someone evicted from the celebrity jungle?

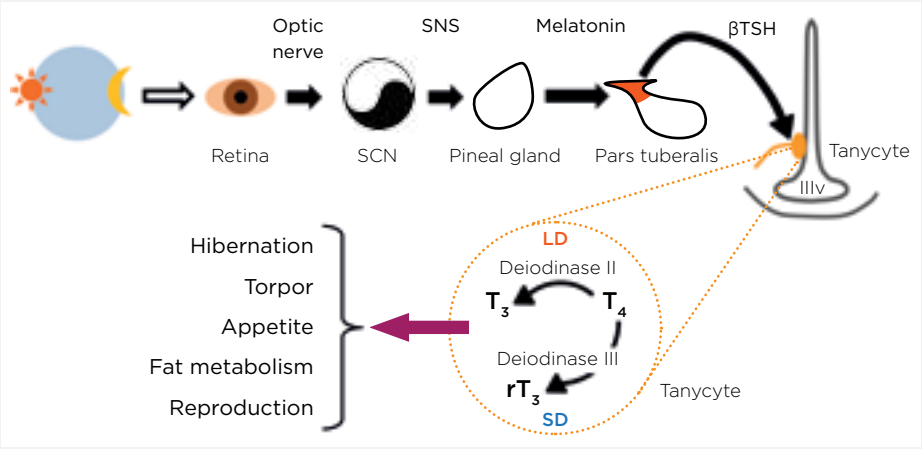
Rather, many small mammals such as shrews and voles enter daily periods of torpor, a hypometabolic state where body temperature drops towards

ambient air temperatures for part of each day, and heart rate decreases hugely. Torpor bouts usually occur during daylight hours, when small mammals would be largely inactive or sleeping at other times of the year.

UNDERLYING MECHANISMS

Our understanding of the neuroendocrine mechanisms that prepare mammals for winter stems from the use of 'model' seasonal species such as the Siberian hamster that can easily be maintained and studied under controlled laboratory conditions. The daily timing of torpor bouts clearly depends upon the suprachiasmatic nucleus in the hypothalamus (see Figure), as hamsters with lesions of this structure still show bouts of torpor when exposed to winter photoperiods, but they occur at random times of day. We also know that the increased duration of pineal melatonin secretion at night provides the crucial neurochemical signal encoding photoperiodic information in mammals.

More surprisingly, research in the last decade has revealed that the pars tuberalis in the pituitary stalk expresses a high density of melatonin receptors in all mammalian species, and is a key site of action of melatonin (Figure). Paracrine signals including the β-subunit of thyroid-stimulating hormone (βTSH) communicate from the pars tuberalis to the adjacent hypothalamus, targeting tanycytes. Another recent discovery is that tanycytes regulate hypothalamic availability of thyroid hormone through differential expression of deiodinase II and III genes.



Schematic summary of key processes underlying winter adaptations. Changes in day length are detected by retinal ganglion cells expressing the photopigment melanopsin, and this information reaches the suprachiasmatic nucleus (SCN) via the optic nerve. The SCN regulates the duration of melatonin secretion from the pineal gland via the sympathetic nervous system (SNS). Melatonin acts on the pars tuberalis of the pituitary stalk, which secretes β-thyroid-stimulating hormone (βTSH). This regulates expression of genes encoding deiodinase enzymes in hypothalamic tanycyte cells that reside in the ependymal lining of the third ventricle (IIIv). In summer long days (LD), expression of deiodinase II results in high local levels of bioactive tri-iodothyronine (T_3), whereas in winter short days (SD), lower expression of deiodinase II but higher expression of deiodinase III results in inactive reverse T_3 (rT_3) (T_4, thyroxine). These central changes in T_3 regulate many seasonal neuroendocrine axes. Credit: F Ebling

Many of the winter adaptations in hamsters and other small mammals depend on a reduced availability of tri-iodothyronine (T_3) in the hypothalamus. Experimentally, the induction of torpor, hypophagia and reproductive regression by short photoperiods can all be blocked by artificially maintaining high levels of thyroid hormone in the hypothalamus. Recent work from David Hazlerigg's lab indicates that the regulation of seasonal neuroendocrine cycles by changes in hypothalamic thyroid hormone availability is an ancestral mechanism common across all vertebrates.

'In preparing for winter, many mammals store huge amounts of fat … Understanding how we can be healthily overweight might be a more tractable approach to managing the obesity epidemic.'

Whilst man is often considered to be a non-seasonal species, reflecting our evolutionary origins in equatorial Africa, there is increasing evidence of underlying seasonal traits in health and well-being. Might these also reflect changes in central thyroid hormone processing?

POTENTIAL TRANSLATIONAL BENEFITS

Understanding the neural and endocrine mechanisms underlying winter adaptations is fascinating biology in its own right, but has potential translational benefits in many areas.

First, in preparing for winter, many mammals become hyperphagic and store huge amounts of fat but, as far as we know, this is not associated with hepatic or muscular steatosis, or with insulin resistance, or with any other morbidities common in obesity. Understanding how we can be healthily overweight might be a more tractable approach to managing the obesity epidemic than proposing lifestyle or dietary changes that simply don't work in the long term.

Secondly, many seasonal mammals then enter a prolonged period of programmed hypophagia coupled with increased fat oxidation. The adaptive value of this for surviving anticipated periods of reduced food availability is obvious, but if we can understand the central mechanisms underlying these traits will this identify novel therapeutic strategies to promote the same outcomes in man?

Thirdly, mammals that hibernate or show daily torpor retain normal brain function despite very hypoglycaemic and hypoxic conditions for prolonged periods. We already exploit hypothermia for some surgical procedures, but understanding the mechanistic basis for this remarkable neuroprotection should surely identify novel therapeutic targets to slow neurodegeneration and protect against ischaemic damage.

FRANCIS J P EBLING (Professor of Neuroendocrinology)
JO E LEWIS (Research Fellow)
School of Life Sciences, University of Nottingham Medical School, Queen's Medical Centre

HOW DO I ... CARE FOR A HORSE WITH 'CUSHING'S DISEASE'?

WRITTEN BY ELIZABETH FINDING

Despite its commonly used name of equine Cushing's disease, the most interesting aspects of equine pituitary pars intermedia dysfunction (PPID) are, in fact, its dissimilarities from Cushing's syndrome, in either humans or dogs. As the recommended name PPID would suggest, this is a disease affecting the pars intermedia of the pituitary gland, not the pars distalis or the adrenal gland. This has repercussions for the best ways of diagnosing and treating the disease.

UNDERLYING PATHOPHYSIOLOGY

Many aspects of the pathophysiology of this disorder are still unknown. However, the basics are relatively undisputed. It is a neurodegenerative disease affecting the periventricular dopaminergic neurones of the hypothalamus.[1,2] Loss of dopamine in the intermediate lobe of the pituitary gland prevents the inhibitory effects of D2 dopaminergic receptor stimulation in the cell membranes of the melanotrophs.

In health, this inhibition results in a decrease in synthesis and release of pars intermedia pro-opiomelanocortin (POMC)-derived peptides and a decrease in melanotroph proliferation. Loss of dopamine-mediated inhibition initially results in hypertrophy and hyperplasia of the intermediate lobe, with an increase in circulating α-melanocyte-stimulating hormone (α-MSH), adrenocorticotrophin (ACTH), β-endorphin and corticotrophin-like intermediate peptide (CLIP).[3] With progression of the disease, the pars intermedia enlarges further, forming an adenoma which can compress adjacent pituitary, hypothalamic and cerebral structures.[4]

The cause of the degeneration of the dopamine-containing nerves is still unknown. There is evidence of accumulation of markers of oxidative stress,[2] misfolded nerve terminal proteins[2] and possibly altered protein clearance,[5] but whether these are causes or consequences of the disease is as yet unproven.

DIFFICULTIES OF DIAGNOSIS

Diagnosis of PPID can be challenging and controversial. As with many progressive diseases, identification of advanced cases is straightforward, but that of early cases is more difficult.

An additional complication specific to equids is related to their adaptation to survival in temperate climates. Horses, and particularly ponies, have an ability to regulate their metabolism to store energy when nutrients are readily available in the spring and summer, in preparation for autumn and winter when nutrients are scarce. Seasonal temperature changes result in the growth of a long hair coat in winter which is shed in the spring. The pars intermedia is involved in these seasonal changes, as is evidenced by the seasonal variation in ACTH and MSH concentrations,[6] cortisol response to dexamethasone suppression[7] and ACTH response to thyrotrophin-releasing hormone (TRH) stimulation.[8,9]

Pony with hypertrichosis.

Studies investigating diagnostic methods are often hampered by the lack of a 'gold standard' ante-mortem test, and those studies using post-mortem diagnosis can also be flawed due to seasonal variation in the histological appearance of the pars intermedia[10] and inconsistencies in histological diagnoses between pathologists.[11] Recent advances in post-mortem diagnosis have been made;[12] using these methods may allow further investigation of ante-mortem tests. The only test which results in no false positives is the presence of hypertrichosis, a pathognomonic clinical sign present in the more advanced stages of the disease.

The current recommendations for diagnosis are based on an algorithm designed by the Equine Endocrinology Group.[13] In animals showing obvious clinical signs of PPID, resting ACTH is the first-line test. If this is high, compared with the seasonally adjusted reference range,[14,15] then treatment should be instigated. If resting ACTH is normal, and in animals with subtle signs of PPID, the TRH stimulation test should be performed and ACTH measured.[16] An exaggerated response is seen in individuals affected by PPID.

Laminitis has long been linked to PPID. The current theory is that hyperinsulinaemia is the main risk factor for laminitis, and PPID may be a risk factor for hyperinsulinaemia. The current recommended test for the risk of clinically significant hyperinsulinaemia is measurement of the insulin response to oral sugar. If an exaggerated response is seen, management to reduce access to pasture and high levels of non-structural carbohydrate feed is required.

APPROACHES TO TREATMENT

Treatment has varied over the years but, since the authorisation of pergolide mesylate for use in PPID in horses in 2011 (Prascend®; Boehringer Ingelheim Vetmedica), the alternatives of cyproheptadine (a serotonin antagonist) and trilostane (an inhibitor of adrenal steroidogenesis) are rarely used.

Pergolide is a dopamine receptor agonist, acting to restore dopamine receptor-mediated inhibition of the melanotrophs of the pars intermedia. Treatment with pergolide reduces basal ACTH concentrations[17] and improves clinical signs in the majority of cases, with the most common side effect being inappetence.[18,19] If pergolide does not result in sufficient improvement, cyproheptadine treatment can be trialled.

IMPROVING THE PROGNOSIS

Whilst treatment can improve the clinical signs and quality of life of horses with PPID, the condition can only be managed and not cured. The disease affects middle-aged to older animals, with varying degrees of the following clinical signs: hypertrichosis, abnormal sweating, predisposition to laminitis and/or infections, loss of muscle mass, lethargy, polyuria and polydipsia.[20] The combination of effective pharmacological and supportive management can anecdotally lead to improved quality of life for several years, although randomised controlled studies are lacking in this area.

Equine PPID has few similarities to human or canine Cushing's syndrome; recognising the differences between the conditions has facilitated progress in the challenging areas of understanding the pathophysiology of equine PPID and how best to diagnose it.

ELIZABETH FINDING
Anatomy Demonstrator, Royal Veterinary College, London

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HOW DO I ... DEVELOP NEW DIABETES DRUGS BY STUDYING NATURAL PEPTIDE HORMONES IN PATIENTS?

WRITTEN BY PHIL AMBERY & LUTZ JERMUTUS

Despite significant investment in genomics and genetics, observations across the illness spectrum – from apparently super-healthy individuals to those with severe disease – have only rarely resulted in new drugs for patients. In metabolic disease, however, there has been at least limited success; the discoveries of insulin, glucagon-like peptide-1 (GLP-1) agonists and sodium–glucose cotransporter-2 (SGLT2) inhibitors all resulted from near-chance observations in dogs and humans.

Banting and Best isolated 'isletin' from pancreatic extracts of dogs and then cattle, to finally demonstrate in patients that insulin was able to keep diabetic patients alive.[1] Observations on the incretin effect and the eating patterns of the Gila monster resulted in the discovery of stable GLP-1 agonists (marketed as exenatide) and from there, based on the human GLP-1 sequence, stabilised variants of the human GLP-1 peptide. Finally, identification of naturally occurring mutations in the SGLT2 transporter, coupled with the effect of phlorizin, led to the discovery of the growing class of SGLT2 inhibitors. Because both the GLP-1 and the SGLT2 inhibitor classes have shown long term cardiovascular, renal and heart failure benefits, all three discoveries may also have in common a likelihood that they will form the basis of modern diabetes treatment in the 21st century.

Although these and other blood glucose-lowering agents have helped us gain some ground in the battle for control of type 2 diabetes, all offer only a delay of disease progression ('treat to fail'), as medication regimens gradually increase while β-cells progressively fail to meet insulin demand and body weight steadily rises. This continues to drive the search for agents that can deliver a step change in weight loss and provide glycaemic control that is as effective as insulin. Such an agent might be able to treat, to cure or at least halt disease progression.

'It's a labour of love to take an observation from the clinic to make a medicine for patients, which requires years of time and millions of pounds to achieve success.'

WHERE NEXT FOR DIABETES RESEARCH?

A possible next step forward in diabetes research might come from work conducted on a still rather less well-known peptide hormone by Steve Bloom's group at Imperial College London in the late 1990s.[2] They researched the effects of oxyntomodulin, a naturally occurring 37-amino acid peptide, levels of which are increased in patients who have undergone bariatric surgery.

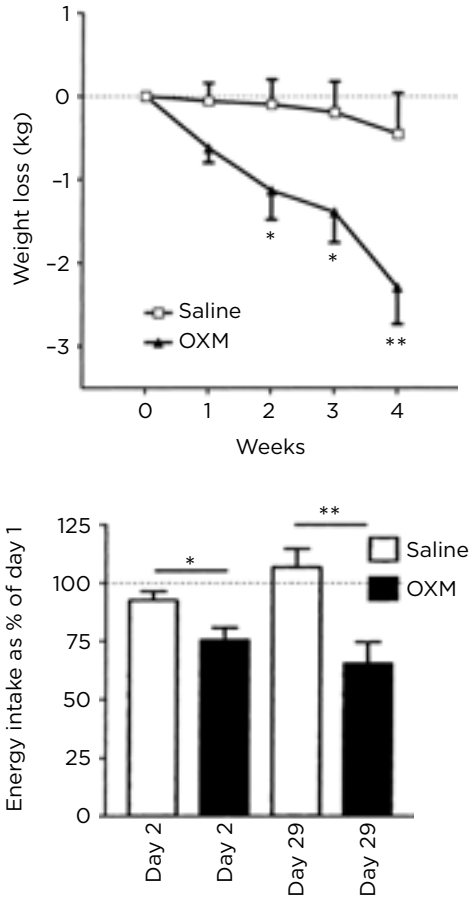
Oxyntomodulin, which is derived from the same gene as GLP-1 but is the result of differential proteolytic cleavage of the pro-peptide, is a dual agonist with both glucagon and GLP-1 activity, with a strong bias toward glucagon. In a 4-week clinical study published in 2005, healthy overweight and obese volunteers were injected with oxyntomodulin 30 minutes before each meal. A weight reduction of 2.3kg was seen, versus a weight reduction of 0.5kg in the comparator group (Figure 1). The larger weight reduction was associated with a reduction in energy intake of 250kcal at the final test meal.[2]

A further study by the same group showed an increase in activity-related energy expenditure, total energy expenditure and overall physical activity.[3] Despite these findings, scepticism about the data persisted because the strong glucagon tone of oxyntomodulin was seen as a significant concern when considering these data for an anti-diabetic therapeutic approach.

MEDIMMUNE ENTERS THE PICTURE

The physical and chemical properties of oxyntomodulin make it a suboptimal choice for an effective drug. It has a half-life in the circulation of less than 12 minutes, is cleaved readily by serum proteases and is very hydrophobic and therefore difficult to formulate. Engineering its stability might have been an easy task, but changing the peptide's serum half-life

Figure 1. Initial observations by Wynne *et al.*[2] on the metabolic effects of oxyntomodulin (OXM). *P<0.05; **P<0.005. Republished with permission of American Diabetes Association, from 'Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial'; *Diabetes* 2005 **54** 2390–2395; permission conveyed through Copyright Clearance Center, Inc.



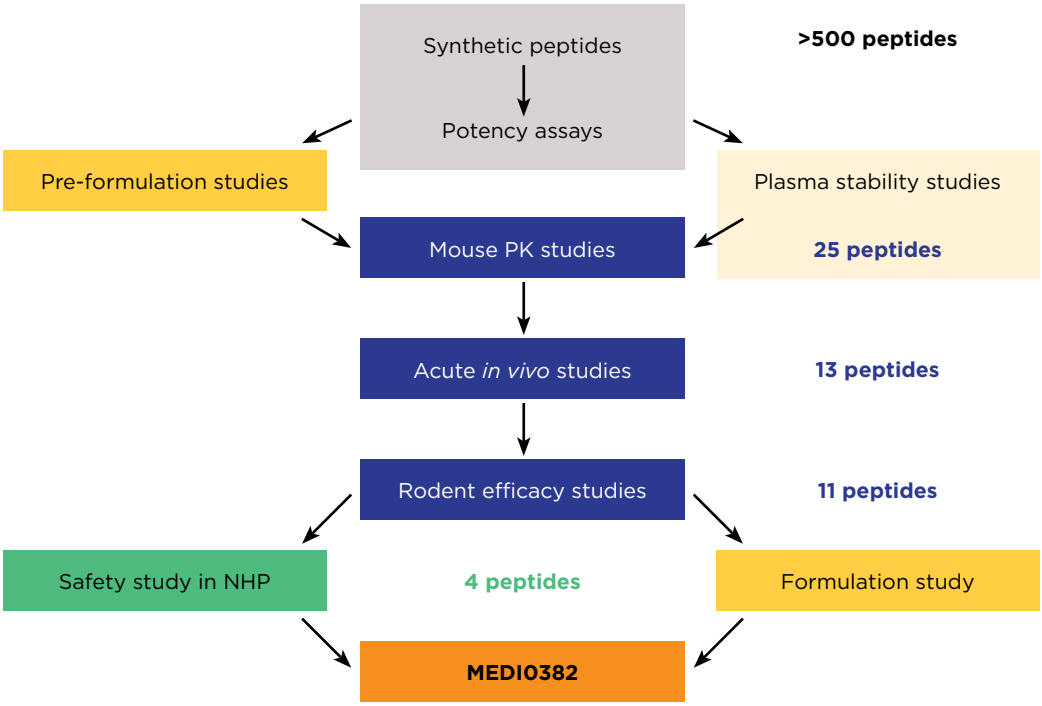


Figure 2. Discovery of MEDI0382, an oxyntomodulin-like peptide for treatment of type 2 diabetes and obesity.[2] NHP=non-human primates; PK=pharmacokinetics.

might require changes to the balance of glucagon and GLP-1 activity to preserve its overall efficacy.

That search, for the optimal oxyntomodulin-like peptide with perfect drug-like properties, was undertaken by MedImmune, the biologics research and development organisation of AstraZeneca. In 2009, MedImmune began to identify drug-like peptides with oxyntomodulin-like activity, also based on literature data that had followed a similar hypothesis.

These peptides were then rigorously tested (Figure 2). Initially, their potency was assessed *in vitro* by incubating them with Chinese hamster ovary cell lines that expressed rodent or human GLP-1 and glucagon receptors. In addition, *ex vivo* studies using primary rodent hepatocytes assessed glucose output to gauge the level of glucagon-like activity and evaluated insulin secretion to gauge the level of GLP-1-like activity.

Natural peptides tend to aggregate and form amyloids when incubated at high concentrations for prolonged periods, because their natural function is to be active at low concentrations and to circulate in the blood for only a few minutes. All peptides were therefore assessed in parallel for their 'manufacturability' and their ability to be formulated and stored at high concentrations.

Preliminary lead peptides were then further characterised in animal models, which are crucial to building confidence in a potential peptide therapy. Studies conducted for the MedImmune lead peptide, MEDI0382, included both acute and chronic administration in rodent disease models and chronic dosing in healthy cynomolgus monkeys to assess safety before being tested for the first time in humans. Many years of work on more than 500 peptide candidates culminated in the selection of MEDI0382 for progression into the clinic,[4] but this is only the next phase of a long journey to become a marketed product.

INTO THE CLINIC

Data on dose ranges of drugs in humans come initially from a single ascending dose (SAD) study. Originally conducted only in healthy volunteers, SAD studies are increasingly conducted in the target population for the drug. In this case, however, because MEDI0382 represents a potential member of a new class of medications for diabetes, studies were conducted in healthy volunteers.

The SAD study is followed by the multiple ascending dose (MAD) study, in which the effect of the drug is properly evaluated in the target population, in this case patients with type 2 diabetes. MAD studies typically involve treating between 40 and 60 patients with the disease. The studies last for a few weeks and are designed to inform the design of the phase 2b and phase 3 study programmes.

With respect to diabetes, the SAD and MAD studies represent the end of the beginning, not the beginning of the end, of the testing programme. To gain a diabetes indication, the potential drug will be tested in an additional 4,500 patients on average in phase 2b and 3 trials, coupled with a cardiovascular outcome study of 6,000 to 9,000 patients. Only when these studies are successfully completed can a drug make it to, and stay on, the market.

CONCLUSION

It's a labour of love to take an observation from the clinic to make a medicine for patients, which requires years of time and millions of pounds to achieve success. Nevertheless, unmet targets for metabolic and endocrine disease remain, and as a medical community it is imperative that we strive to meet them. Pharmaceutical companies are always interested in hearing about potential new targets for therapeutic intervention, and MedImmune is no exception.

PHIL AMBERY & LUTZ JERMUTUS
MedImmune Ltd, Granta Park, Cambridge

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HOW DO I ... DETERMINE CORTISOL DEFICIENCY IN THE CRITICALLY ILL PATIENT?

WRITTEN BY JEREMY W TOMLINSON

There is no doubt that both cortisol excess and cortisol deficiency are associated with increased morbidity and mortality.[1,2] Having an intact hypothalamo-pituitary-adrenal (HPA) axis that can mount an appropriate cortisol response at times of stress and, indeed, critical illness is fundamentally important to survival.

As endocrinologists, we are often faced with an acutely unwell patient. We are asked whether inadequate cortisol production could be contributing to their clinical course and, if so, whether replacement with parenteral hydrocortisone would be beneficial. Whilst the questions are very reasonable and, on the surface, seem straightforward, when one begins to probe both the questions and the published literature a little more deeply, the waters become a little murky to say the least.

WHAT IS A CRITICALLY ILL PATIENT?

The first issue is in defining 'a critically ill patient'. Much of the literature relates to the HPA axis (its assessment and subsequent replacement) in the context of sepsis. However, we cannot necessarily generalise across all conditions. There are many other acute medical and surgical presentations where patients may be critically ill.

Assessment of the HPA axis is complex and, over the last decade, several publications have reported evidence suggesting inadequate cortisol secretion in the setting of critical illness, most commonly septic shock, associated with an adverse outcome.[3] Differing cut-offs for random cortisol measurements, as well as incremental increases in cortisol across the short synacthen test (SST), have been proposed. Furthermore, estimates have suggested that inadequate cortisol responses may be present in up to 60% of patients with sepsis.[4]

INCREASED UNDERSTANDING OF THE HPA AXIS

However, more recently, our understanding of the physiological response of the HPA axis to critical illness and sepsis has changed. There is adrenocorticotrophin (ACTH) resistance at the adrenal gland with elevated circulating levels, which is paralleled by changes in glucocorticoid metabolism. Cortisol clearance is decreased at a tissue-specific level, increasing cortisol half-life and decreasing production rate. In addition, cortisol-binding globulin concentrations are decreased, increasing the bioactive available cortisol.[5]

In this context, interpretation of a one-off, random, circulating cortisol measurement becomes very hard, as does a meaningful assessment of the response to a pharmacological dose of synthetic ACTH.

ASSESSING PATIENTS' INDIVIDUAL NEEDS

Faced with these challenges, one has to adopt a pragmatic safety first approach. In certain situations the 'pre-test probability' of cortisol deficiency is high. These might include patients who are known to have underlying adrenal or pituitary disease, or situations where the pathophysiology of the acute critical illness may cause acute cortisol deficiency (e.g. adrenal haemorrhage, use of etomidate, use of antifungals or CYP3A4 inducers). In these cases, treatment is either mandatory or the threshold for treatment should be very low. Importantly, there is little, if any, evidence that treating with parenteral hydrocortisone is detrimental.

In some patients, there is a high index of clinical suspicion, for example, where there is unexplained hypovolaemia, vasopressor-resistant hypotension, hyponatraemia or hyperkalaemia. In these situations, we are often presented with a random cortisol measurement. Each patient must be assessed individually, but it is reasonable to treat patients with clinical features such as those described above, and a random cortisol lower than 500nmol/l, with parenteral hydrocortisone. Levels higher than this are likely to suggest an adequate adrenal reserve, although the evidence base to confirm this is limited.

The most recent guidelines, published as part of the surviving sepsis campaign, would endorse this approach. They suggest that hydrocortisone should only be considered in individuals who have shock that is resistant to standard therapeutic approaches (and not used at all in the absence of shock). ACTH stimulation tests should not be used and the level of 500nmol/l should be considered as the threshold suggestive of an inappropriately low cortisol level in critical illness.[6]

Finally, this leads to the question of replacement therapy in individuals who have inappropriately low cortisol levels that may be contributing to their clinical presentation. Whilst initial reports had suggested that giving hydrocortisone (and fludrocortisone) replacement improved survival in patients with inadequate cortisol reserve (as measured by SST),[7] a subsequent larger study failed to show any difference in response when stratified by SST cortisol measurement, although in this study only hydrocortisone was administered.[8]

IN SUMMARY

Certainly there is no rationale for the widespread use of hydrocortisone replacement. Bearing in mind the changes in the HPA axis associated with critical illness, there is the potential for replacing with too much glucocorticoid. Administering 200mg hydrocortisone over a 24-h period (as an infusion or as 50mg boluses every 6h) probably achieves a level of cortisol that one might expect in the context of critical illness. Although infusions are recommended as part of the sepsis guidance,[6] there are currently no data to suggest any differences in outcome between the two approaches to replacement.

In conclusion, assessing the HPA axis in critically ill patients is as challenging as ever. Our increased understanding of cortisol secretion, metabolism and action means that the interpretation of isolated cortisol measurements from the circulation must be set in the clinical context in which they are taken. They really only serve as one part of the patient's assessment (alongside clinical judgement), to guide, but not dictate, the necessity of treatment.

JEREMY W TOMLINSON
Professor of Metabolic Endocrinology & Consultant Endocrinologist, Oxford Centre for Diabetes, Endocrinology & Metabolism

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SEX, STRESS AND ADAPTABILITY OF THE DEVELOPING BRAIN:
NEUROSCIENCE NEEDS ENDOCRINOLOGY

WRITTEN BY GLENDA GILLIES

Sex and stress hormones play a critical role in mammalian brain development by regulating the number, location and connectivity of neurones via potent influences on neurogenesis, programmed cell death, neuronal migration and synaptogenesis.

Exposure to testosterone, oestradiol and glucocorticoid hormones (GCs) has to be critically timed and co-ordinated for correct orchestration of brain organisation and correct control of two key processes that are fundamental for survival of the species. These are reproduction and the ability to cope with stress, both of which are differentially programmed in males and females.

As (neuro)endocrinologists, we know that male and female brains develop in different hormonal 'soups' during a critical developmental window for sexual differentiation of the brain.[1] This is largely due to a surge in testosterone production by the male testes at a time when ovarian steroidogenesis in females is relatively quiescent. This occurs during late gestation and the early postnatal period in rats and mice, and probably during mid-gestation in humans.

> ***'We must address the fact that 80% of single sex studies use males, 4% compare both sexes, and some fail to identify sex. It is because of this that most of what we know about the brain actually refers to the male brain'***

Conversion of the testosterone surge to oestradiol by aromatase enzymes in the brain allows the male (but not the female) brain to be exposed to oestradiol. This is a key factor in masculinising/defeminising the circuitry of the hypothalamo-pituitary-gonadal (HPG) axis, which suppresses the ability of the male hypothalamus to respond to oestradiol in adulthood. In contrast, retention of oestradiol sensitivity by the female hypothalamus is necessary for ovulation and reproductive behaviours.

REDRESSING AN IMBALANCE

Neuroscientists studying brain regions other than the hypothalamus have largely ignored brain sex differences, choosing to work with the male of the species to avoid the 'inconvenience' of hormonal fluctuations.

For the population at large, a denial of biological brain sex differences in favour of sociocultural stereotyping may be understandable: equality of the sexes is a hard-fought battle and the concept that the brains of men and women are inherently different, with the implication that one (usually the male) is superior to the other, has been challenged as being politically incorrect and even retrogressive.

However, a decade ago, a review with the wonderful title 'Why sex matters for neuroscience' was, essentially, a wake-up call.[2] It highlighted mounting evidence for biological sex differences in the structure and function of higher brain centres in humans and animals, which influence learning, memory and emotion (hippocampus, amygdala, prefrontal cortex).

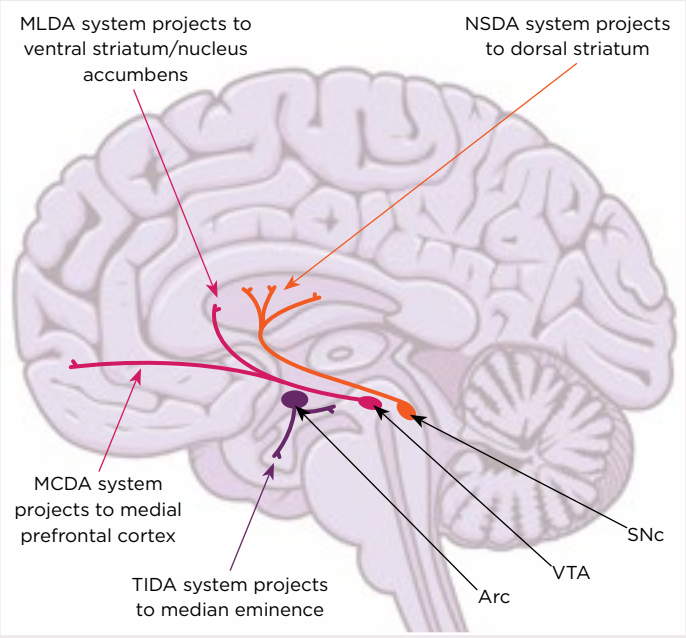


Figure 1. Midbrain dopaminergic systems. Neurones in the substantia nigra pars compacta (SNc) form the nigrostriatal dopaminergic (NSDA) system (involved in sensorimotor regulation) and degenerate in the movement disorder Parkinson's disease. Neurones in the ventral tegmental area (VTA) form the mesolimbic dopaminergic (MLDA) system (involved in reward and feeding) and the mesocortical dopaminergic (MCDA) system (involved in decision making and working memory); their dysfunction is involved in schizophrenia, attention deficit/hyperactivity disorder, autism spectrum disorders, depression and addiction. Arc, arcuate nucleus; TIDA, tuberofundibular dopaminergic system. Brain image ©Shutterstock

Moreover, many of these differences appear to be programmed by the early sex hormone environment and are thought to underpin sex differences that abound in the susceptibility to and nature of virtually all brain disorders. This highlights an urgent need to understand brain sex differences if men and women are to be treated most effectively when brain functioning goes wrong. Therefore, we must address the fact that 80% of single sex studies use males, 4% compare both sexes, and some fail to identify sex. It is because of this that most of what we know about the brain actually refers to the male brain.

THE HPA AXIS

Although not as obvious as the HPG axis, the response of the hypothalamo-pituitary-adrenal (HPA) axis to stress is also sexually differentiated and is often characterised as 'fright, fight or flight' in males, but 'tend, defend or befriend' in females. Sex differences in the developmental sex hormone environment undoubtedly play a role here, as does exposure to GCs, the end products of the HPA axis.

Towards the end of gestation in most mammalian species, both sexes experience a critically timed rise in the bioavailability of GCs released from the fetal/maternal adrenal cortex.[3] This is important for normal maturation of many tissues and organs, including the lungs (hence the value of giving GCs to mothers when premature delivery is threatened) and the brain. Thus, in males (not females), there may be competing epigenetic influences, as GCs briefly overlap with testosterone or its

oestrogenic metabolites on processes that sculpt the developing brain, thereby contributing to normal sexual dimorphisms.

However, if GC levels are inappropriately elevated, either by intrauterine/neonatal exposure to stressors or excessive therapeutic use in perinatal medicine (e.g. repeated courses of GCs may be given when threatened premature birth is delayed, which happens in about 50% of cases), brain structure, function and behaviour may be adversely affected in later life, a phenomenon often termed GC-programming. For example, GCs can interfere with normal brain masculinisation, leading to feminisation of reproductive behaviours, and can also impair HPA axis reactivity to stress and, therefore, physiological stress-coping mechanisms.

'Endocrinology can clearly make important contributions to understanding the origins of brain disorders and their sex bias'

IMPACT ON MENTAL HEALTH

As failure of stress-coping mechanisms is an established risk factor for developing brain disorders, and early-life adversity is linked with mental health problems in later life, many studies have focused on GC programming of HPA axis failure as an underlying mechanism.[4]

However, the mid-brain dopaminergic systems (mDAs; Figure 1) also play a critical role in the behavioural responses to stress, enabling the storage and recall of appropriate coping behaviours. Not surprisingly, therefore, malfunction of dopamine-dependent stress-coping circuitry is a prevalent factor in many neurological and neuropsychiatric conditions. Furthermore, most of these conditions have a non-genetic, developmental component associated with perinatal stress exposure, as well as a sex bias.[5,6]

For example, conditions involving mDAs that affect males more than females include schizophrenia, attention deficit/hyperactivity disorder, autism spectrum disorders and Parkinson's disease, and are associated with stressors such as obstetric complications, exposure of the pregnant mother to natural disasters, famine, death of a loved one, low socio-economic status and infections. Anxiety and depression are more prevalent in females and often associated with childhood abuse.

Our own studies, in rats and mice, exposing fetuses to the synthetic GC, dexamethasone, provide direct evidence that the mDAs are targets for sex-specific GC programming (Figure 2).[3] This profoundly alters the numbers and distribution of dopaminergic neurones and astrocytes in the mid-brain regions of the adult brain. It was accompanied by robust changes in molecular markers of dopamine transmission, but the direction of change was diametrically opposite in males and females for the D1 receptor, the dopamine transporter and dopamine release in response to amphetamine, all of which would predict great effects on behaviours controlled by this circuitry.

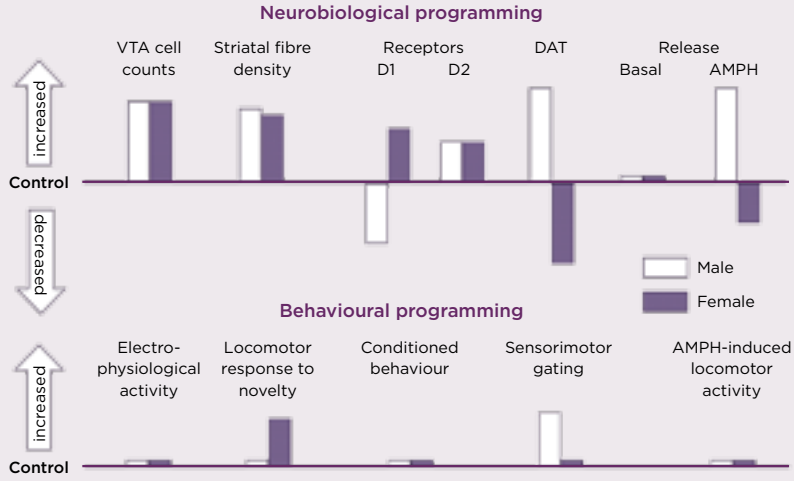
However, this was not the case. Certain behaviours were not affected in either sex, whereas small effects were seen in some behaviours only in males, and in others only in females. We conclude that these changes represent enduring adaptive mechanisms, which secure protection against early environmental adversity. However, there are striking differences by which males and females achieve apparent behavioural resilience, and sometimes these mechanisms fail in a sex-specific manner. These findings show that, although the developing brain can clearly adapt to environmental challenges, it does so at the cost of operating outside normality (allostasis), thereby predisposing an individual to malfunction of stress-coping processes, according to whether you are male or female.

A ROLE FOR ENDOCRINOLOGISTS

Mental health issues are at the top of the agenda, not just for biomedical science, but for governments and global organisations (such as the World Health Organization, the United Nations and charities). There is currently a focus on removing the stigma of discrimination attached to mental disorders, as well as the reluctance of those who suffer from these conditions to come forward for diagnosis and treatment.

Endocrinology can clearly make important contributions to understanding the origins of brain disorders and their sex bias. This is crucial for realising the potential to reverse or prevent these debilitating conditions and for recognising that approaches need to be differentially tailored to the needs of men and women.

Figure 2. Schematic summary of the directional change in neurobiological and behavioural indicators of VTA dopaminergic activity in adult male and female rats after antenatal glucocorticoid treatment. For full details see Virdee *et al.* 2014 *Neuropsychopharmacology* **39** 339–350



GLENDA GILLIES
Emeritus Professor in Neuroendocrine Pharmacology, Imperial College London, Hammersmith Hospital

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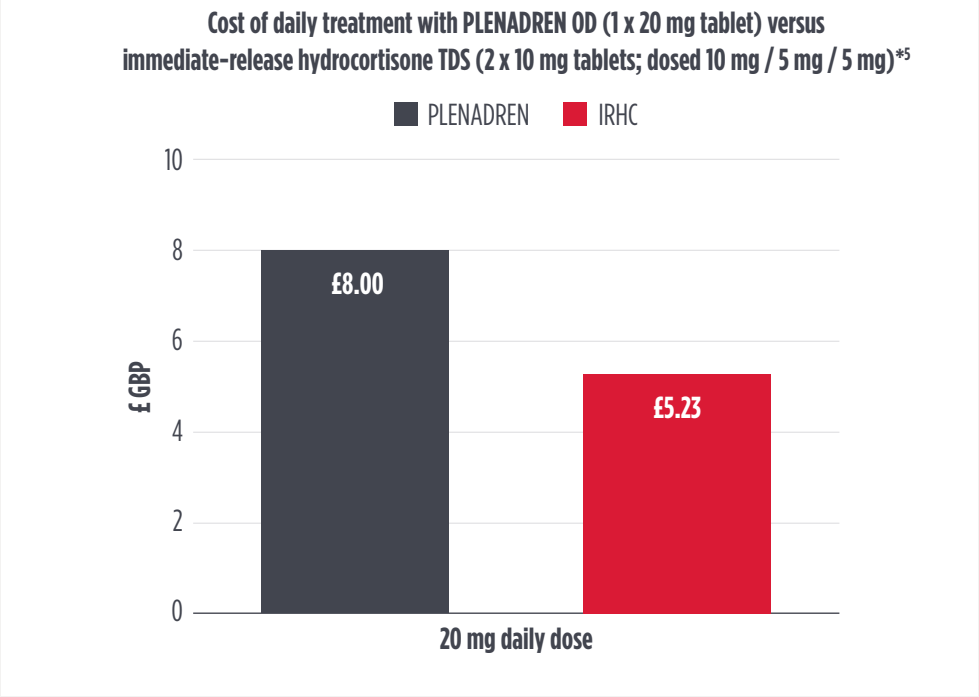
PLENADREN® (Hydrocortisone modified-release tablets) specifically designed for adrenal insufficiency[1–3]

PLENADREN is indicated for the treatment of adrenal insufficiency in adults.[1] PLENADREN offers:

- once-daily (OD) treatment that was preferred by 85% (n=58) of patients over immediate-release hydrocortisone (IRHC) three-times daily (TDS)[2]
- long-term treatment that was generally well tolerated for up to 27 months[3]



*In an interim analysis of the UK cohort of the ongoing Shire EU-AIR registry, the most frequently used daily dose of hydrocortisone was 20 mg, in a total of 47.8% of patients.[4] Costs for 20 mg IRHC TDS are based on 2 x 10 mg tablets (dosed 10 mg / 5 mg / 5 mg). Costs for IRHC treatment may vary depending on the dosing regimen used.

PLENADREN costs as little as £2.77 per day above immediate-release hydrocortisone (typical 20 mg dose)[5]

Adverse reactions (AR) associated with PLENADREN include: Very common (≥1/10): vertigo, headache, diarrhoea, fatigue; Common (≥1/100 to <1/10): nausea, upper abdominal pain, pruritus, rash, arthralgia.[1]

There was an initial increase in the frequency of AR observed up to 8 weeks after first changing from IRHC to PLENADREN. However, these AR (abdominal pain, diarrhoea, nausea and fatigue) are mild or moderate, transient, of short duration, but may require dose adjustment or additional concomitant medicinal products.[1]

References: 1. PLENADREN® Summary of Product Characteristics. **2.** Johannsson *et al. J Clin Endocrinol Metab.* 2012;97:473–81. **3.** Nilsson *et al. Euro J Endocrinol.* 2014;171:369–377. **4.** Shire Data on File: HYD-001v1. March 2016. **5.** BNF November 2016.

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Prescribing Information for PLENADREN® (modified-release hydrocortisone tablets) can be found on the opposite page.
UK/C-APROM/PLE/16/0025

Date of preparation
February 2017

Three new endocrine drugs **APPROVED**

WRITTEN BY JOHN WASS

The Specialised Endocrinology Clinical Reference Group (CRG) is pleased that three of the ten drugs approved in the latest round by NHS England are endocrine-related, namely:

- pegvisomant, a third-line treatment in acromegaly
- pasireotide, for the treatment of refractory Cushing's
- tolvaptan, used to treat hyponatraemia in cancer patients with SIADH (syndrome of inappropriate anti-diuretic hormone secretion) who are awaiting chemotherapy.

We should publically thank Simon Aylwin (London), Dan Flanagan (Plymouth) and Miles Levy (Leicester), who developed the pegvisomant, pasireotide and tolvaptan applications respectively. You can find out more at **http://bit.ly/2b5eQBl**.

This development means that endocrinologists can use these drugs according to fixed criteria.

For pegvisomant, the criteria include: previous surgery and radiotherapy (usually), a lack of biochemical remission with somatostatin analogues, and a documented discussion by a recognised pituitary multidisciplinary team (MDT).

Blueteq technology (the platform for many cancer drugs) will be used. NHS England are developing an electronic pro forma with input from the CRG. The anticipated process will be that an online application will be made after the MDT meeting, and then the prescription will be sent to a home care team. The home care company will deliver the medicine to the patient's address within 10 days. Nursing support to complement this service will be optional, and will include blood tests and disease monitoring. The home care company will invoice the hospital trust. The hospital trust will then cross-charge NHS England.

It is envisaged that details of these patients will be submitted to the acromegaly database.

The CRG is also starting work on parathyroid hormone for hypoparathyroidism.

JOHN WASS
On behalf of the Society's Clinical Committee

DASHBOARD UPDATE

Society members will recall there is now an endocrine dashboard, used by NHS England to try and ensure that there are reasonably efficient systems in place for the assessment of endocrine patients and the various processes involved. As a separate issue, for those endocrinologists involved with the dashboard, it's very important that these are filled in by clinicians as far as possible.

Brighton ROCKED!

Our flagship event, the Society for Endocrinology BES conference, went with a bang in Brighton last November. The 3-day programme attracted more than 1,000 delegates, speakers, chairpersons and exhibitors. We also introduced ePosters for the first time, allowing us to showcase even more high quality endocrinology.

3 days of cutting-edge endocrinology

More than **1,000** attendees

Anyone working in this field should attend.

A great event for learning as well as networking with colleagues.

Highly resourceful, good for networking, a fantastic platform to share current research.

426 abstracts

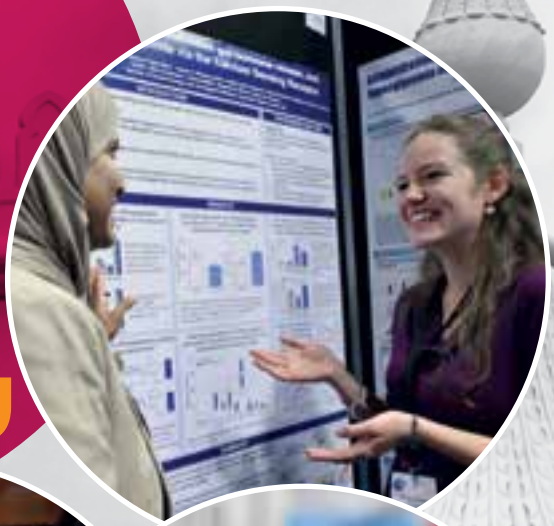
258 posters

116 ePosters

30 prizes awarded for abstracts

It is an excellent opportunity for continuing professional development, to discuss practice with others, find out about new developments which influence clinical care, and mingle with colleagues.

Good overview of endocrinology at both a clinical and a research level.



165 individuals tweeting (#SFEBES2016)

671 tweets

589 articles in the press

As a clinical endocrinologist and translational scientist, it gives me the perfect mix.

The best annual meeting for endocrinology worldwide and the best value for money.

A useful way to get an update across the whole spectrum of endocrinology.

Up to date evidence on common conditions and insights into the rarer ones.

FIND MORE ONLINE

You can get the latest Society events and training information at: **www.endocrinology.org/events**

SAVE THE DATE

Society for Endocrinology BES 2017
Harrogate, UK, 6–8 November

www.endocrinology.org/events/sfe-bes-conference/sfe-bes-2017

What's in it for you?
THE VALUE OF JOINING A SOCIETY COMMITTEE

Society for Endocrinology committees underpin all the Society's activities. For example, our Clinical Committee helps develop clinical practice, supports clinical research and inspires clinical education and career development, while our Public Engagement Committee develops our outreach strategy, and oversees our programme of public events and related training opportunities for members.

To ensure we provide the best support to all our members – be they clinicians, nurses or basic scientists – it is important that a diverse range of people are involved. Being a committee member allows you to make an impact on the discipline, informing how we support endocrinologists, and championing endocrinology to the wider world. It's also a great opportunity to grow your network of contacts to develop your own career.

Several committee vacancies need to be filled from January 2018, and we encourage members from all backgrounds and career stages to apply.

So, what's it like to be on a Society committee? Find out as three of our committee members share their experiences.

JOIN A SOCIETY COMMITTEE AND MAKE A DIFFERENCE

Opportunities are coming up on the following committees from the end of 2017. The deadline for nominations is 30 June 2017. Please consider putting your name forward – we welcome applications from Society members of all backgrounds and career stages.

- Clinical Committee
- Corporate Liaison Board
- Early Career Steering Group
- Finance Committee
- Nurse Committee
- Programme Committee
- Public Engagement Committee
- Science Committee

You can learn more about the remit of each committee, and details of how to apply, at **www.endocrinology.org/about-us/governance**. If you have any informal queries, please contact Julie Cragg (**members@endocrinology.org**).

STEPHANIE BALDEWEG

Stephanie is Clinical Lead of the Department of Diabetes & Endocrinology at University College London (UCL) Hospital, and Consultant Physician in Diabetes & Endocrinology and Honorary Senior Lecturer at UCL. She is a current member of our Clinical and Public Engagement Committees.

WHY DID YOU DECIDE TO GET INVOLVED WITH THE SOCIETY'S COMMITTEES?

Like many of my colleagues, I have greatly benefited from the Society for Endocrinology's excellent work, and decided I wanted to give something back and contribute more actively to shape the Society's activities. Colleagues suggested that I should apply to be on the Clinical Committee. This definitely piqued my interest, as I had enjoyed founding and working on the National Guideline Group for Emergency Management of Pituitary Apoplexy, as well as being interested in teaching, clinical education and career development.

I realised that the Public Engagement Committee might also be closely aligned with my interests. My enthusiasm in this area has resulted in my involvement locally and nationally with patient support groups (I am a Trustee of The Pituitary Foundation) and I was looking for an opportunity to apply this on a wider scale.

I applied to both committees with strong support from my colleagues. I was hoping for more involvement in the Society, working with like-minded people, learning new things/adding variety to my professional portfolio and applying my skills to benefit the endocrine community.

WHAT DOES BEING A COMMITTEE MEMBER INVOLVE?

You need to attend a set number of meetings a year. These are usually very stimulating and rewarding as projects come to fruition. Throughout the year there are actions from meetings and often additional email discussions and phone calls to help to move projects along.

On the Public Engagement Committee I helped develop the Society's public engagement strategies, shaping the website and other resources, overseeing and participating in public engagement events (e.g. the BMA career fair) and learning more about press involvement.

On the Clinical Committee I was involved in developing clinical guidelines and contributing to strategies and events focused on teaching, clinical education and career development.

WHAT'S YOUR EXPERIENCE OF BEING A COMMITTEE MEMBER BEEN LIKE?

I have greatly enjoyed being a member of both committees, and have benefited from and contributed to the exchange of ideas. Different viewpoints on many topics from colleagues across the country and from people in a number of organisations have shaped my thinking on the future of education in endocrinology.

HAS BEING ON THE COMMITTEES BROUGHT YOU ANY BENEFITS?

It has without doubt been beneficial to my personal development, giving me a sense of contributing to our endocrine community. I have learnt much from others, both junior and senior, and have enjoyed the exchange of ideas. I have been able to shape events and strategies using my expertise. I have fine-tuned my non-clinical skills and have brought many ideas back to my local hospital trust, directly benefiting my patients and colleagues.

KIM JONAS

Kim is a Lecturer in Reproductive Physiology at St George's University of London. She currently sits on our Science Committee and the Editorial Board for* The Endocrinologist. *In the past, she chaired our Early Career Steering Group and sat on our Public Engagement Committee.

WHY DID YOU DECIDE TO GET INVOLVED WITH THE SOCIETY'S COMMITTEES?

My first postdoc mentor, Rob Fowkes, encouraged me to join the Young Endocrinologists' (YE) Steering Group (now the Early Career Steering Group) when a call for members was announced. If I'm totally honest, I joined not really knowing what to expect! But I knew that I wanted to contribute to the Society for Endocrinology and to be actively involved in the YE Steering Group – 'the voice of my peers' – to enable me to represent the YE demographic within the Society.

WHAT DOES BEING A COMMITTEE MEMBER INVOLVE?

This very much depends on the remit of the committee concerned. Over the years, I've served on the YE Steering Group, the Public Engagement Committee and, currently, the Science Committee and the Editorial Board of *The Endocrinologist*. Each has very different requirements, but all require attendance of two or three meetings per year, plus email communication in between.

For the Science Committee, my main tasks are marking grant applications, contributing symposium ideas for the Society for Endocrinology BES conference, and responding to policy documents received on an ad hoc basis. For *The Endocrinologist*'s Editorial Board, the role involves contributing ideas for the quarterly magazine, writing articles and hot topics, and suggesting/inviting people to write articles for each issue.

WHAT'S YOUR EXPERIENCE OF BEING A COMMITTEE MEMBER BEEN LIKE?

I can truthfully say that it has been a hugely positive experience. You get to see the ins and outs of how the Society works, and understand why and how the organisation evolves. It's been great to be a part of positive changes that have been implemented: for example, the instigation of the Early Career Grants, and the establishment of the YE Quiz (now the Early Career Quiz) at the Society for Endocrinology BES conference. Both these things have been a huge success for the Society and the YE demographic. I've also had the opportunity to meet some fantastic people along the way, which has been a great added bonus of committee membership.

HAS BEING ON THE COMMITTEES BROUGHT YOU ANY BENEFITS?

One of the major benefits has been the networking opportunities. This has been particularly valuable at this early stage of my independent career, establishing collaborations and having people to support and review grant applications.

KATE LINES

Kate is a Postdoctoral Research Scientist at the Oxford Centre for Diabetes, Endocrinology & Metabolism, University of Oxford. She is the incoming chair of our Early Career Steering Group.

WHY DID YOU DECIDE TO GET INVOLVED WITH THE SOCIETY'S COMMITTEES?

I applied to be on the Early Career Steering Group in the third year of being a postdoc. I had attended the Society for Endocrinology BES conference the previous year, where I also went to the Early Career Quiz. I was sharing an office with a member of the Science Committee, and when I mentioned the Quiz they said there was a vacancy on the Early Career Steering Group and suggested I should apply. Having been on the social committee where I did my PhD, I thought it would be a good opportunity to interact with other early career researchers and carry on organising events.

WHAT DOES BEING A COMMITTEE MEMBER INVOLVE?

The primary responsibilities are coming up with suggestions for our session at the Society for Endocrinology BES conference, organising the Early Career Quiz and thinking of ways to support the Society's early career members, such as setting up and maintaining a Twitter account. We attend two meetings a year in Bristol. We are also involved in other activities, including writing articles for *The Endocrinologist*, judging the SfE BES Junior Poster Prize and attending events, such as the Parliamentary Links Day.

WHAT'S YOUR EXPERIENCE OF BEING A COMMITTEE MEMBER BEEN LIKE?

I have really enjoyed it, so much so that I have now agreed to become the Chair and serve for a further 2 years! Interacting with the other committee members and the early career researchers, as well as the Society's staff, has been really fulfilling. It has also been very rewarding to see our suggestions recognised: for example, seeing the speakers you suggested on the programme at the Society for Endocrinology BES conference, and the introduction of the Junior Poster Prize for Student members.

HAS BEING ON THE COMMITTEE BROUGHT YOU ANY BENEFITS?

In addition to being enjoyable, it has been a great opportunity for networking with more senior endocrinologists, and so getting both myself and my work recognised. It has also given me the opportunity to chair sessions at the Society for Endocrinology BES conference and to take part in public engagement activities. These are very useful to have on your CV.

Your Society in 2016: **A YEAR OF SUCCESS!**

In 2016, the Society for Endocrinology continued to go from strength to strength. We worked with our members, authors, reviewers, partners and the public to support our aim of advancing endocrinology.

We are looking for members to join many of our committees from January 2018, to continue our work. If you'd like the opportunity to help make a difference to your Society and the wider world of endocrinology, find out how to put yourself forward at **http://bit.ly/2iB3Vp8**. You can also read about what it is like to be a Committee member on pages 22–23.

Endocrine Connections is scheduled to receive its first impact factor in 2017. To celebrate this important milestone, the Society for Endocrinology is delighted to offer its members completely free Open Access publishing in *Endocrine Connections* in 2017,* a saving of £950 per publication.

We are proud to offer this special member benefit to our members and encourage you to support the journal in its aim to be the leading Open Access title in the field.

Find your member number on email correspondence and submit your next paper at **www.endocrineconnections.com**.

***Terms and conditions**

1. The corresponding author must have been a member of either SfE or ESE for one calendar year on the date of submission to be eligible.
2. The offer is available for papers submitted between 1 January and 30 September 2017.
3. All submissions are subject to peer review and the usual acceptance criteria.
4. The offer applies to individual members and is not open to corporate members.

Recognising and rewarding **EXCELLENCE!**

The Society has a long history of honouring individuals who have significantly helped advance endocrinology. The award of a medal by the Society reflects scientific excellence, a wide contribution to the discipline and the high impact of an individual's research. We are delighted to announce our 2017 medallists, who will present their plenary lectures at the Society for Endocrinology BES conference 2017, 6–8 November in Harrogate.

DALE MEDALLIST
Professor Andrew Hattersley, Exeter

JUBILEE MEDALLIST
Professor Julia Buckingham, Uxbridge

SOCIETY MEDALLIST
Professor Antonio Vidal-Puig, Cambridge

STARLING MEDALLIST
Professor David Hodson, Birmingham

TRANSATLANTIC MEDALLIST
Professor Teresa Woodruff, Chicago, IL, USA

EUROPEAN MEDALLIST
Professor Marian Joëls, Utrecht, The Netherlands

INTERNATIONAL MEDALLIST
Professor Andrew Arnold, Farmington, CT, USA

NOMINATE OUR MEDAL WINNERS FOR 2018

Seven medals are awarded by the Society every year. We would like to hear who you feel should be recognised for their contribution to the field.

All nominations for 2018 medallists will be considered for a shortlist by the Nominations Committee before the final selection is approved by Council.

For details of the medal remits and how to nominate, visit **http://bit.ly/SfEmedals**.

Deadline for nominations: **16 June 2017**

NOMINATE A NURSE

The Society's Endocrine Nurse Award recognises endocrine nurses who have demonstrated innovative and successful nurse-led initiatives to advance best practice in research, education or patient care.

We congratulate Nikki Kieffer (Leicester), the winner of the inaugural award in 2017.

As a Society member, you can nominate any endocrine nurse who is also a member of the Society and who you feel is worthy of the 2018 award. All nominations will be considered by a panel of members including our Nurse Committee.

You can find further details at **http://bit.ly/SFENurseAward**.

Deadline for nominations: **16 June 2017**

THYROID ENDOCRINE NETWORK

WRITTEN BY PETROS PERROS & CARLA MORAN

The Society's Thyroid Endocrine Network (which we call 'Thyronet' for short) aims to:

- act as a catalyst for collaborative thyroid research
- interface with the Society's Clinical Committee
- advise the SfE Programme Committee
- suggest topics for guideline development.

One of our first priorities has been to establish communication channels between Network members. We now have a JISCMail account (**SfE-thyronet@jiscmail.ac.uk**), a Twitter account (**@SfE_thyronet**) and a Facebook page (Society for Endocrinology Thyroid Network).

GRANT SUCCESS

In May 2016, we were awarded a Society grant for a thyroid-focused Regional Clinical Cases Meeting. It took place in Cambridge last October, and was an innovative, interactive and popular event that attracted trainees and consultants and received excellent feedback.

In addition, the British Thyroid Foundation awarded us a grant at the end of 2015 to look at 10-year survival and recurrence rates for patients with differentiated thyroid cancer by disease stage. Preliminary data for a cohort diagnosed in 2002 so far indicate 2% disease-specific mortality at 10 years and 6% recurrence rates for patients with differentiated thyroid cancer, 50% of whom had stage II–IV disease.

We have also submitted a successful application for a Clinical Endocrinology Trust grant, led by Bijay Vaidya, on anti-thyroid drug-induced agranulocytosis.

OTHER ACTIVITIES

We are about to conduct a survey to assess the clinical experiences of Network members regarding the recent price increase in liothyronine (tri-iodothyronine, T_3) and how this has affected clinical practice.

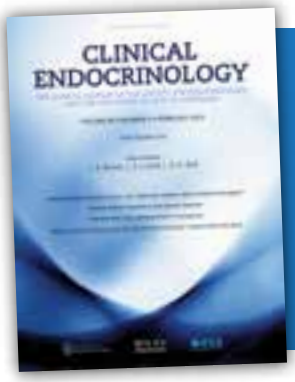
May 2017 will see the British Thyroid Association's annual meeting, and we are working closely with them to finalise the programme for the Trainee Day component of this event. The Network has also submitted suggestions to the Programme Committee for the Society for Endocrinology BES conference in November 2017.

Network members have made suggestions for a number of national observational studies, including projects on myxoedema coma, thyroid storm and one-stop thyroid nodule clinics, which we aim to implement in the next 12 months. We also plan a 'brainstorming' meeting, to prioritise research proposals, and we hope to formulate at least one prospective clinical study and one basic/translational proposal and submit these to funding sources.

The Network welcomes new members. Please get in touch if you are interested.

PETROS PERROS & CARLA MORAN
Network Leads

Find out more at **www.endocrinology.org/endocrinenetworks** or contact **members@endocrinology.org**.



CLINICAL ENDOCRINOLOGY DISCOUNTS AUTHOR PUBLICATION CHARGES

The publishers of the Society's official journal *Clinical Endocrinology* offer a significant discount on author publication charges to members who wish to publish their papers in the journal using open access.

You will need to enter a code (found in the members' area of the Society for Endocrinology website) when completing the OnlineOpen form on the Wiley site.

CLINICAL EXCELLENCE AWARDS

The Society successfully supported several members in this awards process last year and we will again be offering support to those of you who wish to apply for an award in 2017. You will find details on our website once they have been announced by the Advisory Committee on Clinical Excellence Awards.

SfE BES 2016 ONLINE

A selection of sessions from the 2016 SfE BES conference are now available to view online via the Society's website. These include plenary lectures from names such as Steve Bloom, Jason Carroll and Tim Korevaar, and futures sessions providing insight and tips on how to progress your endocrine career. You can also watch our very popular topical debate between Karim Meeran and Stafford Lightman on whether prednisolone should be the first line of treatment for glucocorticoid replacement in adrenal insufficiency. Visit **www.endocrinology.org/careers/careers-resources/videos/videos-from-sfe-bes-2016** to find out more and subscribe to our YouTube channel.

Society for Endocrinology
STUDENT AMBASSADORS

COULD YOU BE A STUDENT AMBASSADOR?

Are you a Student or pre-PhD Scientist-in-Training member? Would you like to promote awareness of endocrinology throughout your institution?

If so, join our Student Ambassadors scheme to act as a voice for your fellow students and help advance awareness of endocrinology. Full details of the initiative, along with an application form, are available at **http://bit.ly/2jMvOqs**.

MEMBERSHIP RENEWAL

Have you renewed your membership for 2017? If not, it will lapse at the end of March and you will no longer be a member of the Society, which will affect your eligibility for any grants. Renew online now at **www.endocrinology.org/membership/join-or-renew**.

HOW TO MANAGE AS A NEW CONSULTANT

WRITTEN BY DOMINIC CAVLAN

Recent issues of *The Endocrinologist* have outlined some helpful ways to negotiate specialty training, but haven't yet tackled what to do when the final ARCP (Annual Review of Competence Progression) hurdle has been vaulted, and you stumble over the finishing line into that first consultant role. In the modern parlance, what follows are some 'lifehacks', or shortcuts, to ease that first year.

THE RIGHT TOOLS FOR THE JOB

The worst aspect of specialty training is the paperwork, with the spectre of unticked ePortfolio boxes an eternal haunting presence, only relieved by the hope that it will, one day, all be over. I'm afraid that this is a forlorn dream, as the reward for ePortfolio completion is to be made responsible for half a dozen more. Advice such as 'Don't do what I did' will only take supervisees so far, so some formal training early on is a good idea.

As a bonus, you will also be signed up to your trust's own particular appraisal programme. If used correctly, this has the potential to be one of those rare sequels that is better than the original. You may previously have regarded those colleagues who were capable of coherently answering the question 'Where do you see yourself in 5 years?' with justifiable suspicion. If used correctly and with the right support, the appraisal process can actually help you figure this out and plan to get there. There is no upside to the use of job-planning software, however; this will require the help of someone your trust has seconded from NASA.

MAKING IT PERSONAL

First impressions count in any new job, but even more so when you aren't going to be moved on in 6 months. It is therefore vitally important to learn everyone's names, as they could be your colleagues for the next 30 years.

Establish oneself as a benevolent presence by sending a few people home in the first week if they look as though they may have a cold. This is the equivalent of an old fashioned centre-half getting a 'reducer' in early in a football match to show they mean business. Publicly insisting that the registrar who was your fellow trainee a few months ago now address you as 'Dr Smith' is likely to make the wrong sort of first impression, even where that is your actual surname.

DON'T SUFFER IN SILENCE

Autonomy and responsibility are two sides of the same coin. Expect to come down with a virulent strain of 'imposter syndrome' early on, but don't suffer alone. Your new consultant colleagues won't think you're a fraud if you ask them for advice. In a meeting, if there is something you don't understand, but you think you should really know by now, you're allowed to ask for clarification 'for the students in the room'.

Learning how to properly manage a case for its own sake, and to look after a patient well, is a much more rewarding experience when it doesn't have to be linked to a curriculum. Take advantage of your junior colleagues here, by expecting them to report to you on the latest guidelines for management of submassive pulmonary embolism, for instance, before you will sign their CPD request.

'Autonomy and responsibility are two sides of the same coin. Expect to come down with a virulent strain of 'imposter syndrome' early on, but don't suffer alone.'

FOLLOW YOUR INCLINATIONS

The standard advice meted out to new consultants is to be careful not to say 'yes' to everything, lest you find yourself in committee meetings to decide on who should supply new light bulbs for the outpatients' department. There is truth in this, but it's just as important to seek out areas that you are really interested in, to start to carve out a niche.

If teaching is your passion, for instance, find out who is in charge of medical students on the firm, and if they're ready to pass that baton on. If you have a flair for IT, and you're convinced that the new electronic record system can't really be as bad as everyone says, volunteer to help fix it. If you take on these types of role with one eye on a future clinical excellence award, rather than for their own satisfaction, you may find that they're more of a burden than a pleasure.

MAINTAIN A BALANCE

Finally, a national conversation about physician burn-out is thankfully starting to take place in the UK. Establishing a healthy work–life balance right at the outset of a consultant career will serve you well in this regard. Not taking paperwork home with you is key, so proper planning of your SPA (supporting professional activity) time is vital.

Cultivating those hobbies and relationships that took a backseat during the itinerant life of a registrar will also make an important contribution, although after you've paid the General Medical Council for your full registration you might not quite have the funds to do so straightaway.

DOMINIC CAVLAN
Barts Health NHS Trust, London

SURVIVING THE FIRST YEAR OF A LECTURESHIP

WRITTEN BY MATTHEW SIMMONDS

Within any scientific career there is one constant: change. Moving from a PhD to being a postdoc requires constant evolution, to establish yourself as an independent researcher. Obtaining a position as a lecturer is, for many, a natural next step.

A year ago, I took up the role of Senior Lecturer at the University of Lincoln. This position involves both teaching and research, in contrast to my previous research-focused positions, which had some teaching on the side. Whilst I was extremely excited to join the University of Lincoln and their expanding diabetes research group, I was slightly daunted to be at a university which was ranked in the UK's top 10 for both student satisfaction and teaching within four of the six undergraduate courses run by our school.

I am sure everyone, including my boss, would like to hear that my transition into this new role was seamless. However, to be honest, it has (at points) been a steep learning curve, albeit an enjoyable one. Now, a year on, I have come up with 12 top tips on how to survive your first year in a lectureship.

'Don't be surprised if the students don't ask many questions in your early lectures … It takes time for them to get to know you, but it will happen much more quickly than you think.'

1. DON'T PANIC

Any change in position is challenging. At some point you will think (as I did), 'Will I ever get the hang of this?' But, take it from me, you will be fine.

2. FIND YOUR LECTURING STYLE

We all lecture differently, so don't be afraid to try different styles. One thing I learnt is that you WILL make some mistakes, but these will help you improve your technique. Speaking to your mentor, attending teaching courses and obtaining a teaching qualification can also provide you with further support.

3. ALLOW TIME TO CREATE LECTURES

Initially you will be working out what style to use, balancing text with video and pictures, and determining the optimal number of slides for a lecture. Give yourself plenty of time to do this, as you will need it. Eventually you will refine your style and spend less time creating lectures.

4. GET FEEDBACK FROM YOUR PEERS

Whilst scary – there is nothing more nerve-racking than presenting in front of new colleagues – this can provide great insights into your teaching. Initially, I stuck to the lecture podium like glue. Once I was made aware of this, I started to move more, enabling me to further engage with the students. Do, however, be aware of potential trip hazards (although that is a story for another day).

5. MAKE USE OF ELECTRONIC SITES

Sites such as Blackboard and Turnitin can be used to give feedback, submit coursework and communicate with students. Investing time in getting used to them is really worthwhile. (If you get stuck, YouTube has some excellent 'how to' videos.)

6. ARRIVE EARLY TO CHECK THE TECHNOLOGY

Technology will occasionally fail, however good your IT department is. Getting to the venue early allows you to ensure everything is working and to get help if necessary. If things can't be fixed instantly, just explain this to your students. You'll be surprised how easily you work around this.

7. ESTABLISH LECTURING EXPECTATIONS

Identifying these early on (e.g. by putting lecture slides up in advance and ensuring students sign registers etc.) will enable you to put steps in place to help meet these, such as creating lecture upload deadline reminders.

8. MAKE USE OF YOUR MENTORS

Discuss any concerns with the mentor your university provides. Don't be afraid to ask 'stupid' questions (I ask a LOT of these). Establishing a good rapport with your mentor will provide you with a better understanding of your institution.

9. GO TO TEAM MEETINGS AND EXAM BOARDS

It is worth going to all of these early on, even before you have students to discuss at them, as they will increase your understanding of how they work, for future reference.

10. GET SUPPORT IN ACTING AS A TUTOR

Most lecturers will be assigned tutees. Tutees can talk to you about any concerns they may have about their degree and if they encounter any issues that may affect their academic performance. Before undertaking this role, establish what support systems are in place in your university, so you can direct your tutees to the correct place to get help.

11. DON'T WORRY IF POPULARITY TAKES TIME

Don't be surprised if the students don't ask many questions in your early lectures, or if you put in third year research projects when you first start and only a few people are interested. It takes time for the students to get to know you, but it will happen much more quickly than you think.

12. KEEP YOUR RESEARCH GOING

If you are moving institutions it can take longer to re-establish your research than you would like. When combined with new teaching demands, it can be tricky. Remember it's a key part of your position, so just keep going and use any potential 'downtime' to finish papers, look for new collaborations and put in applications for funding.

After my first year, I can honestly say there is nothing better than seeing students engaging with your lectures, and combining this with the research you love. Whilst I do not claim to know everything about this position yet, I have really enjoyed it. I hope these tips provide an insight for anyone who decides to make a similar move now or in the future.

MATTHEW SIMMONDS
Senior Lecturer, School of Life Sciences, College of Science, University of Lincoln, Joseph Banks Laboratories

A F.I.N.E IDEA: ENCOURAGING INTERNATIONAL COLLABORATION IN NURSING

WRITTEN BY LISA SHEPHERD & KATE DAVIES

The idea for the Federation of International Nurses in Endocrinology (F.I.N.E) was conceived at the joint International Congress of Endocrinology (ICE) and ENDO 2014 meeting held in Chicago, IL, USA.

Initially, F.I.N.E had nurse representatives from the UK, USA, Australia and New Zealand. It has since expanded to represent nurses globally, including colleagues from Belgium, Switzerland, The Netherlands, Germany, Turkey, China, Vietnam and India to name a few, and includes both adult and paediatric nurses.

EARLY SUCCESS

At the first meeting, it was agreed that the education and training of endocrine nurses would be a fundamental aspect of F.I.N.E, and that inclusion of nurse programmes at learned Society meetings was important.

'The group's mission is to promote excellence in clinical care by advancing the science and art of endocrine nursing throughout the world.'

One of the group's first objectives was to develop a nurse programme for ICE 2016 in Beijing, China in collaboration with the Chinese Society of Endocrinology. This bore fruit last September, when ten nurses presented material at the conference. They included colleagues from the UK, China, USA, Belgium, Vietnam and Australia, and encompassed paediatric and adult perspectives, as well as diabetes and endocrinology.

The programme was a great first success. It was relevant not only to nurses in endocrinology, but also to healthcare professionals working in areas with no experience of endocrine specialist nurses. Links with these healthcare professionals have now been made, and aspects of practice and future collaborative work have commenced.

Of course, a visit to the Great Wall of China is a must do in Beijing (pictured), and the F.I.N.E nurses all had a great trip.

A group of nurses take the opportunity to visit the Great Wall of China during the meeting in Beijing.

The group visited Professor Karen Lam and her team at Queen Mary Hospital in Hong Kong.

DELIVERING F.I.N.E'S VISION

F.I.N.E's vision for the future is to create 'An accessible global network of nurses in endocrinology promoting optimal health outcomes for people with endocrine disorders'.

The group's mission is to promote excellence in clinical care by advancing the science and art of endocrine nursing throughout the world. F.I.N.E will support this through the professional development of nurses in endocrinology practice, interdisciplinary collaboration, research and education. Our collective membership will seek to raise awareness of endocrinology practice with the global public.

We took our first steps in collaboration by visiting the Queen Mary Hospital in Hong Kong on our way to ICE 2016 in Beijing. Here, Professor Karen Lam kindly hosted our day-long visit. The team took time out from their busy schedules to show us the typical daily practice for endocrine and diabetes nurses in one of Hong Kong's busiest hospitals, and we appreciated their very warm welcome. While practice does differ greatly around the world, it is encouraging to see that nurse-led services are reaching all corners of the globe!

LOOKING TO THE FUTURE

The conference in Beijing certainly has been the highlight of our endocrine careers to date. The nurse presenters had all worked very hard, and the work we are doing around the world really is inspiring.

We continue to look forward to collaborating with one another, and would welcome more input and membership from other endocrine nurses from around the world. Here's to ICE 2018 in Cape Town, South Africa!

LISA SHEPHERD
Chair, SfE Nurse Committee
Endocrinology Advanced Nurse Practitioner, Heart of England NHS Foundation Trust

KATE DAVIES
Member, SfE Nurse Committee
Senior Lecturer in Children's Nursing, London South Bank University

If you would like to contact the Federation of International Nurses in Endocrinology, please email Chris Yedinak (**yedinakc@ohsu.edu**) or Lisa Shepherd (**lisa.shepherd@heartofengland.nhs.uk**).

LISA SHEPHERD

NURSE COMMITTEE CHAIR

Endocrinology is one of the most fascinating specialties to work in as a nurse (although I know I am biased!). The roles can vary widely from one nurse to another. Some nurses work as part of a large team, whilst other nurses work alone.

The Society for Endocrinology has created a Facebook group, which is quick and easy to join and allows nurses to communicate and interact with one other, no matter where they are based in the endocrine community. Those of you who are keen users of social media can also follow the endocrine nurses on Twitter. You will find details for joining both these groups on this page.

Raising standards, promoting excellence in nursing and reaching out to fellow endocrine nurses is important, not only nationally but also internationally. The mission of the Federation of International Nurses in Endocrinology (F.I.N.E) is to do just that. F.I.N.E proudly developed and presented a nurse programme at the 17th International Congress of Endocrinology (ICE 2016) which was held in collaboration with the 15th Annual Meeting of the Chinese Society of Endocrinology last year. You can read more about this work in the article written by Kate Davies and myself on page 29.

Continuing on the theme of excellence in nursing, we look forward to Nikki Kieffer receiving the inaugural Endocrine Nurse Award and delivering her presentation at Endocrine Nurse Update on 20–21 March in Birmingham. There is still time to register if you have not already done so via the Society's website. I look forward to seeing you there for what promises to be an interesting and interactive programme.

LISA SHEPHERD

Nominations are now open for the 2018 Endocrine Nurse Award. Visit the Society's website for more details.

KEEP IN TOUCH WITH COLLEAGUES

Keeping in touch with fellow endocrine nurses is often difficult. This is why the Society has created a private Facebook group just for nurses. The group will enable you to network with other members of your specialty and hold private discussions within the group.

Once you have joined you will able to expand the existing community of over 60 nurses by adding your nurse friends. All nurses who work in endocrine-related areas are welcome to join – there is no need to be a member of the Society for Endocrinology.

Join us by emailing **nurses@endocrinology.org** and we'll send you an invitation.

Do you use Twitter? Follow Endocrine Nurses **@Soc_EndoNurses** for the latest updates and information.

GENERAL NEWS

BURSARY SUPPORTS WORK IN THYROID EYE DISEASE

The Thyroid Eye Disease Charitable Trust (TEDct), a charitable patient support organisation, aims to create greater awareness of thyroid eye disease as well as to inform and support those affected by this condition.

TEDct
Thyroid Eye Disease
Charitable Trust

TEDct is offering a bursary of up to £500 to nurses and other healthcare professionals who work regularly with patients with thyroid eye disease in the UK. This will support their education (e.g. by paying for conference/course fees and associated travel/accommodation expenses), to enhance their work with patients with thyroid eye disease.

Please see **www.tedct.org.uk/bursary** for further details, including the application form.

ENDOCRINE SURGERY MEETING

The 7th Symposium of the European Society of Endocrine Surgeons will take place in Oxford, UK on 6–8 April 2017. You can find out more information at **www.eses17.com**.

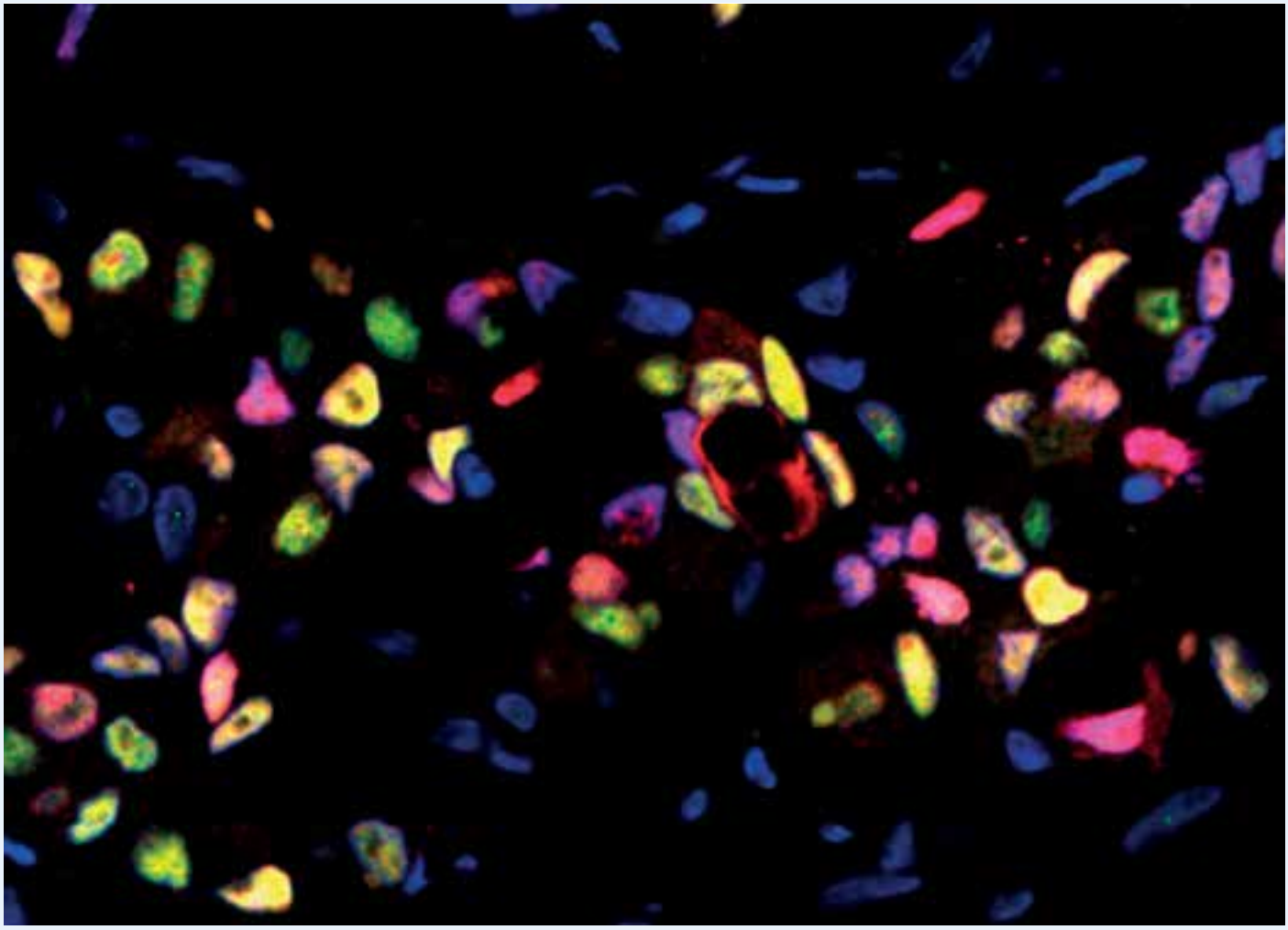
Images in ENDOCRINOLOGY

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

COVER IMAGE FROM *ENDOCRINE-RELATED CANCER*

DECEMBER 2016

The image depicts double immunofluorescence localisation of full length androgen receptor (AR, red) and a constitutively active, truncated AR variant (AR-V7, green) in a tissue section derived from an oestrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor-2 (HER2)-positive infiltrating breast carcinoma from a postmenopausal woman. Most cells express detectable levels of AR-V7 along with full length AR. *Credit: G Tarulli (University of Adelaide, Australia).*



Enter our Cover Art Competition

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

Visit **www.endocrinology.org/news** for more information.

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WHO ARE BIOSCIENTIFICA?

Bioscientifica provide events, publishing, and association management services to learned societies within the biosciences. We are owned by the Society for Endocrinology, and share our parent company's values. We are therefore uniquely placed to help learned societies realise their strategic ambitions.

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Contact Kate Sargent:
conferences@bioscientifica.com

www.bioscientifica.com/event-management

@Bioscientifica