

THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

Endocrinology and evolution:
**THE TREE OF LIFE
EDITION**

SPECIAL FEATURES **PAGES 6-14**

From the deep ocean
**THYROXINE'S HIDDEN
HISTORY**

P6

A hypoglycaemic mystery with...
VINCENT MARKS

P24

Lessons to learn?
**TEACHING IN HIGHER
EDUCATION**

P30

**SUPPORTING
YOUR CAREER**
New Society
training initiatives

P17

STUCK IN A RUT?
Try an Early
Career Grant

P20

UK NURSES INSPIRE
Competency Framework
triggers new Nurse
Federation

P22

A WORD FROM THE EDITOR...



Welcome to this special animal issue of *The Endocrinologist*. Inside, you will see that we have a great deal to learn from other species. Siggie (my nine-month-old Cockapoo) has been a little distracted since I told her that Cushing's disease is common in poodles. In fact, I have also learnt that very senior members of our Society have pets that are currently suffering from acromegaly, thyrotoxicosis and Cushing's – we will soon be starting an agony aunt page!

The main thrust of this edition is comparative endocrinology. My Biology teacher at school (Dr Applin – hugely influential with a legendary comb-over) once set us an essay entitled 'Discuss how ontogeny recapitulates phylogeny' (it took me several weeks to work out what it meant). He was trying to engrain in us the idea that embryology informs us about evolution - it has stuck with me ever since. It explains many of the quirks of endocrine anatomy, physiology and molecular biology. Janine Danks' group from Melbourne has been exceptionally supportive of this issue. You will read about the evolutionary biology of thyroxine, parathyroid hormone and CRH. You will also learn about obesity in dogs and thyrotoxicosis in cats. This issue also contains an interview with Vincent Marks, of hypoglycaemia fame. At 84 years of age, Vincent is still a very vibrant presence and gives a fascinating account of medicine in the post-war period.

So as the leaves turn brown, the nights draw in and the football season is well under way (come on Arsenal), we can look forward to an exciting endocrine run-in to Xmas. Many thanks as always to everyone who has contributed to this magazine, and long may it continue.

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CONTENTS

You can view this issue online:
www.endocrinology.org/endocrinologist

ON THE COVER...

P6-14 COMPARATIVE ENDOCRINOLOGY

Lessons learnt from
distant relatives

AN INTERVIEW WITH...

P24-27 VINCENT MARKS

From G&T to crime scene:
the highs and lows of
hypoglycaemia

HEADLINES

- 3** New European movement
Clinical Committee Chair
Editorial Board vacancies

HOT TOPICS

- 4** The latest endocrine research

OPINION

- 15** From our Science Committee and
Career correspondents
16 A Young Endocrinologist in parliament

SOCIETY NEWS

- 17** Society support for education and training
18 Journal news
19 Engaging the public: sex, diabetes
and cancer
20 Would you benefit from an Early
Career Grant?

NURSES' NEWS

- 22** New Federation of International Nurses
in Endocrinology

GENERAL NEWS

- 28** New guidelines
Book review

FEATURES

- 29** **To BAT or too fat?**
Our award-winning
undergraduate essay

- 30** **Teaching in higher education:**
Rosemary Bland
seeks improvement

AND FINALLY...

- 31** **Images in endocrinology**

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

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

Deadline for news items for the Winter 2014/15 issue: 26 September 2014.

Deadline for news items for the Spring 2015 issue: 12 December 2014.

Front cover image ©123RF STOCK PHOTOS



SOCIETY JOINS NEW EUROPEAN MOVEMENT

The European Society of Endocrinology (ESE) has announced the creation of the ESE Council of Affiliated Societies (ECAS), which will allow the 44 national societies associated with ESE to participate much more in ESE's activities. ECAS will be a new voice for endocrinology in Europe, with the aims of promoting the role of endocrinologists in tackling global health issues and raising the profile of hormone science. As an ESE Affiliated Society, the Society for Endocrinology will be a member of this group and we look forward to bringing you more news about this initiative shortly.

NEW CLINICAL COMMITTEE CHAIR



We are pleased to welcome Professor Wiebke Arlt (Birmingham) as the Chair of the Society's Clinical Committee. Professor Arlt takes over from Professor Jayne Franklyn (Birmingham) who has skilfully led this committee over the last 4 years. We thank Professor Franklyn for her commitment and expertise during this time.

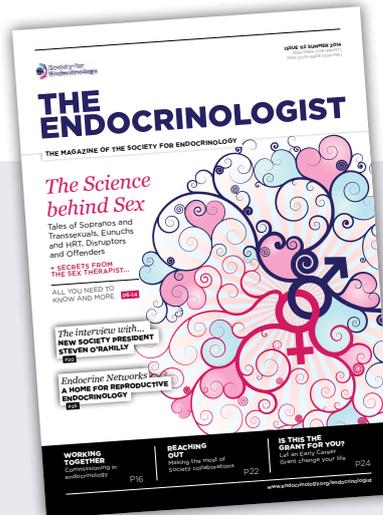
CONFERENCE AWARDS 2014



Acrobatics, comedians and plenty of champagne greeted members of the Society team at the Conference Awards 2014, held in London in June. Society for Endocrinology BES 2013 was a finalist in the 'Best Development of an Existing Conference - UK' category. The award entry was submitted by Bioscientifica who manage the conference and the rest of the Society's events programme. Unfortunately the team missed out on the award this year, but was thrilled to be recognised among such high competition.

NEW PAPER FROM CaHASE

A new paper has been published from the Society's Congenital Adrenal Hyperplasia Adult Study Executive (CaHASE) project, which seeks to examine the needs, care and treatment of adult patients with congenital adrenal hyperplasia (CAH) to inform best practice. CaHASE is funded by the Clinical Endocrinology Trust. This latest study examined the relationship between final height and health outcomes in CAH patients. You can read it in *Journal of Clinical Endocrinology & Metabolism*, <http://dx.doi.org/10.1210/jc.2014-1486>. More information on the CaHASE project is available at www.endocrinology.org/about/projects/cah.html.



JOIN OUR TEAM!

We're looking for new Editorial Board members to join *The Endocrinologist* team, starting in January 2015. We want to hear from basic scientists, clinicians and nurses at all career stages who have a passion for communicating endocrinology and want to work with us to ensure *The Endocrinologist* continues to develop to be the premier magazine for endocrinologists. The term of office is 2 years and you will be expected to attend two meetings per year, with additional work carried out via email. Further information and application forms are available at www.endocrinology.org/endocrinologist.

Thank you to everyone who completed our recent questionnaire on *The Endocrinologist*. We will bring you the results in a future issue.



SOCIETY CALENDAR

17-19 October 2014
CAREER DEVELOPMENT WORKSHOPS
Eastwood Park,
Gloucestershire

3-5 November 2014
CLINICAL UPDATE
Manchester

5 December 2014
REGIONAL CLINICAL CASES MEETING
Birmingham

12 January 2015
OBESITY UPDATE
London

18-20 February 2015
ESE BASIC SCIENCE COURSE IN REPRODUCTIVE ENDOCRINOLOGY
Edinburgh

26 February 2015
NATIONAL CLINICAL CASES MEETING
London

2-4 November 2015
SOCIETY FOR ENDOCRINOLOGY BES 2015
Edinburgh

see www.endocrinology.org/meetings for full details



GRANT AND PRIZE DEADLINES

27 November 2014
EARLY CAREER GRANTS

15 December 2014
CONFERENCE GRANTS

11 February 2015
UNDERGRADUATE ESSAY PRIZE

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

WITH REGRET

We are sorry to announce the death of Senior Member Professor David Hadden of Belfast, UK. A full obituary will appear in the next issue.

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 www.bioscialliance.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

Bisphenol A alters kisspeptin neurone activity

Endocrine-disrupting chemicals (EDCs), such as bisphenol A (BPA), are found in many household and industrial products and are a source of concern for human health. BPA exposure has been associated with reproductive diseases including polycystic ovary syndrome, premature delivery and recurrent miscarriage. In animal studies, BPA disturbs hormonal levels, alters the oestrous cycle and impairs reproductive capacity.

Wang *et al.* investigated the mechanisms by which BPA disrupts reproduction and the hypothalamic-pituitary-gonadal (HPG) axis. By administering BPA

orally or directly to the anteroventral periventricular nucleus (AVPV) and arcuate nucleus (ARC), they found that BPA augments the ER α -mediated stimulation of AVPV neurone kisspeptin expression and release. Interestingly, BPA altered AVPV kisspeptin neurone activity only at the pro-oestrous stage of the oestrous cycle and had little effect on the ARC kisspeptin neurones. Further work is required to fully define the molecules and signalling pathways that interact with BPA to disrupt the HPG axis.

Read the full article in *Journal of Endocrinology* **221** 201–213

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Biological pathways mediating short stature

Several genetic disorders are associated with primordial short stature. One is 3-M syndrome, which exhibits severe pre- and postnatal growth restriction but with no significant disorder of other systems. Mutations in *CUL7*, *OBSL1* and *CCDC8* have been associated with 3-M syndrome, although it is not clear how these genes contribute to growth.

Hanson and colleagues used a 'systems' approach to predict biological pathways that may be involved by identifying proteins that interact with *CUL7*, *OBSL1* and *CCDC8*. They identified a 3-M protein network with over-representation

of the mRNA splicing/processing pathway, and showed that mRNA splicing is altered in 3-M samples compared with controls.

This provides evidence for mRNA splicing, ubiquitination and the IGF signalling pathway in growth, and the dysfunction of these pathways in 3-M syndrome. Further work will determine how these pathways contribute to growth, but the generation of a 3-M protein 'interactome' provides a useful tool to identify candidate proteins for future studies.

Read the full article in *Journal of Molecular Endocrinology* **52** 333–344 (OA)

ENDOCRINE-RELATED CANCER

RANK and c-Met mediate prostate cancer metastasis

Aggressive prostate cancers are androgen insensitive and metastasise to other sites, including bone, which is both painful and lethal. There is evidence for a role of RANKL expression in inducing epithelial-to-mesenchymal transition and bone and soft tissue homing in non-metastatic cancers of breast, lung and kidney.

Chu and colleagues investigated the role of RANKL in the metastasis of prostate cancers to bone. RANKL-RANK-mediated signalling, along with c-Met, downregulated androgen signalling, making prostate cancer cells more aggressive and metastatic, and consistently caused colonisation of metastases to bone. RANK-mediated signalling also promoted expression of numerous genes through the upregulation of key transcription factors. This potentially enables

cell reprogramming, generating an altered cell phenotype that promotes cancer cell growth and survival in bone. Expression of RANKL also enabled prostate cancer cells to recruit and transform non-metastatic bystander cells to bone.

This suggests an important role for RANKL in cancer metastasis to bone. Further investigations must determine whether this signalling pathway is a useful therapeutic target.

Read the full article in *Endocrine-Related Cancer* **21** 311–326 (OA)

ENDOCRINE HIGHLIGHTS

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

Hormone replacement interactions with antiepileptic drugs

Patients who have had neurosurgical interventions or neurological problems may have hypopituitarism and also be at increased risk of seizures. Will use of anti-seizure medication in this situation interact with the various hormone replacement therapies used, or vice versa?

Paragliola and colleagues have carefully examined whether specific hormonal axes are affected. They have discovered substantial evidence of effects on thyroid hormone metabolism; excessive thyroid hormone replacement may, for example, reduce the seizure threshold. Sex steroid hormones and their metabolites can directly affect neuronal excitability and behave as neurosteroids. Also, medications such as carbamazepine can alter the renal clearance of drugs such as desmopressin, which may therefore warrant a dose reduction in the context of central diabetes insipidus. Caution and awareness of such factors are important in these scenarios.

Read the full article in *The Lancet Diabetes & Endocrinology* (doi: 10.1016/S2213-8587(14)70081-6)

Anti-diabetic activity of insulin-degrading enzyme inhibitors

Insulin-degrading enzyme (IDE) may be a useful target to treat type 2 diabetes, as its inhibition would elevate insulin levels. Support for this hypothesis includes genetic studies identifying IDE as a diabetes susceptibility gene. However IDE knockout mice show impaired glucose tolerance despite increased insulin levels.

Maianti and colleagues identified a small chemical molecule inhibitor of IDE, allowing investigation of the effect of transient inhibition of IDE on glucose tolerance tests. During oral glucose tolerance tests, this resulted in improved glucose tolerance and slower gastric emptying. In contrast, IDE inhibition and administration of glucose via intraperitoneal injection led to impaired glucose tolerance, suggesting that IDE modulates other glucose-regulation hormones in addition to insulin. The authors show that IDE also regulates the abundance and physiological effects of amylin and glucagon and that improved glucose tolerance following intraperitoneal administration can be achieved by ablation of glucagon signalling.

Inhibition of IDE may be a viable therapeutic option for type 2 diabetes, either administered transiently during meals, or combined with other therapies to generate synergistic effects.

Read the full article in *Nature* **511** 94–98

CLINICAL ENDOCRINOLOGY

Remission of prolactin-producing pituitary adenomas after pregnancy

This retrospective study by Domingue *et al.* took data from 73 women with prolactinoma and assessed remission post-pregnancy after a median follow up of 22 months. Seventy patients were on medical treatment before becoming pregnant, when treatment was discontinued. Patients who needed to restart dopamine agonists later in pregnancy were excluded from the analysis.

Approximately 40% of patients were in remission at the last follow-up visit (46% of microprolactinomas and 26% of macroprolactinomas). Factors

predicting remission included prolactin concentration and adenoma size at diagnosis, prolactin level prior to pregnancy (on medical treatment) and normalisation of pituitary MRI after pregnancy. However, small adenoma size at diagnosis and normal MRI post-pregnancy were independently associated with chance of remission using a multivariate analysis statistical model. Lactation and its duration as well as number of pregnancies were not predictive of remission.

Read the full article in *Clinical Endocrinology* **80** 642–648 (OA)

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Corticosteroid treatment of non-islet cell tumour-induced hypoglycaemia

Mohammedi *et al.* report a 77-year-old woman who presented acutely with reduced consciousness and glucose of 1.2mmol/l. She had a diagnosis of a malignant solitary fibrous tumour treated with non-curative surgery and chemotherapy 6 years previously. Her HbA1c was normal (37mmol/mol) and she had not suffered hypoglycaemic episodes/symptoms before. She was not diabetic or receiving medications known to cause hypoglycaemia. A mass arising from her chest wall was identified by radiography, in keeping with her known history of malignancy. Head CT and routine bloods were unremarkable. Her insulin and C-peptide concentrations were appropriately suppressed in the presence of hypoglycaemia.

IGF-I was low; however, electrophoresis revealed an abnormal high molecular weight band corresponding to an incompletely processed IGF-II precursor.

A diagnosis of paraneoplastic hypoglycaemia driven by IGF-II mediated insulin-like activity was established. Treatment with glucose infusion and daily intramuscular glucagon injections did not correct glucose levels. Hypoglycaemia was successfully managed with high dose corticosteroids initially, followed by a reducing dose regime.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* 2014 EDM140026

ENDOCRINE CONNECTIONS

Androgen influence on autoimmunity

Gonadal steroids appear to modulate autoimmune diseases in humans and animal models. Olsen *et al.* used a genetic variation in the androgen receptor (AR) gene to assess whether androgen signalling influences development of lupus disease in females. They previously found that decreased AR signalling in males with lupus was associated with greater incidence of autoimmune symptoms.

In contrast, here they found the reverse, with diminished signalling associated with decreased severity of autoimmune symptoms. There was no influence of androgen signalling on the predisposition of patients to develop lupus.

Currently, most evidence suggests androgen signalling is immunosuppressive. Several recent studies, such as this, show an increase in immune activity with androgen signalling, suggesting our understanding of the interaction of gonadal steroids with the immune system is incomplete and needs to be determined.

Read the full article in *Endocrine Connections* **3** 99–109

Evolutionary constraints on the glucocorticoid receptor

Understanding the processes that have led to the generation of diverse, complex, living organisms is central to evolutionary biology. Using protein reconstruction, directed evolution and biophysical analysis, Harms and Thornton describe the evolution of the glucocorticoid receptor (GR). They show that this was non-deterministic, requiring the acquisition of two rare permissive mutations under non-selecting conditions. This suggests the evolution of GR would be unlikely to follow the same route in similar conditions. Overall protein evolution depends on the structural architecture of the protein and the mechanisms by which protein function is acquired.

Read the full article in *Nature* **512** 203–207

Genetic basis of bilateral macronodular adrenal hyperplasia

Bilateral macronodular adrenal hyperplasia (BMAH) accounts for less than 1% of Cushing's syndrome. Familial forms with autosomal dominant inheritance patterns have been identified. About half of cases of BMAH have germline mutations in the *ARMC5* gene. Somatic, second hit-mutations of *ARMC5* have also been found in a subset of adrenal tumours.

Gagliardi *et al.* studied five BMAH kindreds using Sanger and whole exome sequencing in peripheral blood and resected adrenal nodules. In four, mutations in *ARMC5* were found, including two novel variants. There was a lack of phenotype-genotype correlation and some family members carried the mutation without clinical evidence of BMAH. Somatic mutations in coding regions of *ARMC5* were only found in one resected adrenal nodule, thus suggesting that somatic mutations could reside in other (non-coding or regulatory) regions of *ARMC5* or, indeed, in other genes. Genetic screening of *ARMC5* could detect relatives in BMAH families who would benefit from clinical screening. However, the penetrance of BMAH in *ARMC5* mutation-positive individuals is unknown and further longitudinal studies in BMAH kindreds are needed.

Read the full article in *Journal of Clinical Endocrinology & Metabolism* (doi: 10.1210/jc.2014-1265)(OA)



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Novel hormone regulating immune-adipose interactions

Exercise increases energy expenditure and is beneficial in resisting obesity and metabolic disorders. It also reduces adipose tissue inflammation, which may play a role in reducing insulin resistance and improving glucose homeostasis. Certain hormones are released from muscle during exercise, increasing their circulating levels, and potentially contributing to exercise's therapeutic effects.

Rao and colleagues have identified a novel hormone, meteorin-like (Metnl), which is induced in muscle after exercise and adipose tissue following exposure to cold. Metnl was shown to link the immune system to adipose tissue function via recruitment of eosinophils into adipose tissue. This activity increases levels of interleukin-4 (IL4) and IL13, promoting activation of adipose tissue macrophages and resulting in the increased expression of thermogenic and anti-inflammatory pathways in fat.

These actions lead to increased energy expenditure and improved glucose tolerance, beneficial effects in the treatment and/or management of metabolic disease. The therapeutic potential of Metnl requires further investigation.

Read the full article in *Cell* **157** 1279–1291

THYROXINE: AN EARLY HISTORY

WRITTEN BY JAMES FALCONER SMITH

'If nothing else, knowledge of the extraordinary complexity of all life forms should engender a level of humility that has been lacking in the medical profession for generations and which, combined with the ability to listen and to spend an appropriate length of time with patients, represents the very essence of the art of medical practice.'

PROFESSOR DAVID WEATHERALL



Jellyfish in dark blue water

©123RF STOCK PHOTOS

IODINE

The story of thyroxine starts long before man first walked on the Earth. I will begin with iodine. This halogen element was first isolated by Bernard Courtois in 1811 and named by Sir Humphrey Davy 2 years later, but its origins are very much earlier.

All elements, with the exceptions of hydrogen and helium, are produced within stars by the processes of nucleosynthesis. Elements up to atomic number 26 (iron) are formed as stars steadily shine. This contrasts with elements with higher atomic numbers (e.g. iodine, atomic number 53), which are only formed in the cataclysmic events of a supernova explosion. Iron atoms are hurled at speeds up to 10% of the speed of light through the outer layers of an exploding star, where they collide with lighter atomic nuclei and, in doing so, create the heavier elements.

These products form part of the interstellar dust which may later form accretion discs. In due course, these condense to form stars and circling planets. Thus the Earth, the Moon and every one of us is literally made of stardust. You might consider the birth or death of a star to be a rare event, but it has been calculated that around 300 million stars are born and die *each day* in the whole observable universe. Around one million of these will end in a supernova explosion.

Iodine is a comparatively heavy element and in the molten primordial Earth it gravitated towards the inner iron core. Thus it is relatively sparse in the outer crust, where it makes up just 0.00005%. Deep magma circulates up to emerge in outpourings such as volcanoes and to power deep underwater vents, where iodine concentrations are higher. Iodine combines with other substances in seawater to form iodates and other iodine-containing molecules. These will combine spontaneously, and it is not too big a leap to suggest that the first thyroxine molecule was formed in the vicinity of an underwater vent. When was this? The honest answer must be that we do not know, but there are a few clues. Thyroxine is used by a number of sea-dwelling organisms, some of which have been around for a very long time indeed.

THYROXINE IN THE SEA

Strobilation is a form of asexual division in cnidarians (e.g. jellyfish) which has remained unchanged for at least 480 million years. It is thyroxine-dependent. However, the jellyfish does not synthesise thyroxine. It appears to concentrate it from the surrounding seawater. Thyroxine has thus been conserved through long evolutionary time and its function has been adapted from species to species.

THYROID GLAND EVOLUTION

During evolution, organisms may have become accustomed to a supply of iodotyrosines and iodothyronines derived from external sources, and eventually developed a requirement for iodinated amino acids. The first evidence of an organ capable of providing iodothyronines, and therefore related to the vertebrate thyroid, is found in the protochordates, amphioxus and ascidians. This organ, the endostyle, lies on the floor of the pharynx and connects with the pharynx by a duct. An endostyle is still present in the lamprey larva or ammocoete. Interestingly, lamprey larvae have high levels of thyroid hormone and there is then a fall in levels that triggers metamorphosis – in complete contrast to amphibia in which the reverse is true.

During metamorphosis of the ammocoete into the adult lamprey, the endostyle loses its connection with the pharynx and becomes a thyroid composed of scattered follicles. These follicles are not encapsulated, but they have the typical biosynthetic functions associated with hormone formation in the adult vertebrates. It has been stated that the significant evolutionary event was the development of iodination centres within the endostyle.

The most primitive vertebrates in which a follicular thyroid gland can be definitely demonstrated are the jawless fishes (agnathans). I suggest that the progression of creatures from sea-living to land-based has produced a requirement for the synthesis and storage of iodine-containing compounds since they are moving into an environment with low iodine levels.

There is a relationship between the thyroid and the gastrointestinal tract. Ciliated thyroid cells have been found in the mouse and the shark, a reminder of the origin of the gland from endoderm. In mammals, the gastric mucosa and the salivary glands retain a functional relationship to the thyroid in that they too can concentrate iodide, and the salivary gland contains a peroxidase.

Most thyroid glands (other than in man) only synthesise thyroxine, not tri-iodothyronine (T3) and rely exclusively on peripheral conversion to produce T3. This allows marked variation in T3 concentrations in different parts of the body, depending on deiodinase distribution, which may be important (for example) in amphibian metamorphosis. In man, thyroid hormone binds to both cell surface receptors (in common with most hormones) and to receptors on the cell nucleus. This is another a sign of an ancient evolutionary origin.

THYROXINE AND THYRONAMINES

Thyronamines are breakdown products of thyroid hormones that have physiological effects in some animals. A fall in thyroxine or thyronamine levels is associated with a variety of physiological changes, especially hibernation. Whilst such falls might be a secondary change, there is evidence that they are the main trigger in at least some mammals, e.g. ground squirrels.

Hibernating bears have been extensively studied. Free thyroxine levels are lower during hibernation, but thyrotrophin (TSH) levels are little changed. There is an exaggerated response to TSH-releasing hormone (TRH) during hibernation, and it has been suggested that bears have a hypothalamic hypothyroidism during this period.

THYROID HORMONE-BINDING PROTEINS

In parallel with the evolution of hormone molecules, there are significant variations in thyroid hormone-binding proteins between species. Albumin has been found to be a thyroxine carrier in the blood of fish, amphibians, reptiles, monotremes (e.g. the platypus), marsupials, eutherians (all placental mammals) and birds. Thyroxine binding to transthyretin (previously called pre-albumin) has been found in the blood of eutherians, birds and some Australian marsupials, but not in blood from fish, toads, reptiles and monotremes. Thyroid hormone-binding globulin (TBG) appears to be a late arrival on the scene and is only found in some mammals.

In summary, the thyroid axis is a very primitive endocrine system and is highly conserved in evolution, underpinning its vital role to life. There are important differences and similarities in the evolutionary biology of the thyroid gland among species, and studying this area may give us new insights into the role of this vital gland in human beings.

JAMES FALCONER SMITH
Consultant Chemical Pathologist,
University of Leicester

FURTHER READING

1. Dumont J *et al.* 2011 *Ontogeny, Anatomy, Metabolism and Physiology of the Thyroid*. <http://bit.ly/1p4NnBj>.
2. Knight JD 2013 *Deep Sea Hydrothermal Vents*. <http://bit.ly/WWsdel>.
3. Hellgren EC 1998 Physiology of hibernation in bears *Ursus* **10** 467–477 (<http://bit.ly/1o6p5qh>).

DIVERSE USES OF THYROXINE

ORGANISM	ROLE OF THYROXINE	MILLIONS OF YEARS SINCE FIRST APPEARANCE ON EARTH
Gorgonian coral (cnidarian)	Normal spicule formation	550
Jellyfish (cnidarian)	Strobilation (asexual division)	480
Frog (amphibian)	Metamorphosis from tadpole to adult	360
Salmon and rainbow trout (fish)	Regulation of smoltification, adaption from fresh water to salt water	165
Red-headed bunting (bird)	Pre-migratory fattening	55
Spotted munia (bird)	Feather regrowth after moult	55
Penguin (bird)	Annual catastrophic moult	55
Human	Maintenance of normal metabolic rate etc.	0.2



Red-headed bunting, *Emberiza bruniceps*

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HOW OLD IS PARATHYROID HORMONE? MUCH OLDER THAN ANYONE THOUGHT...

WRITTEN BY JANINE A DANKS



Fuller Albright, whose clinical studies on parathyroid hormone (PTH) underpin our understanding of mineral metabolism, proposed in the 1940s that humoral hypercalcaemia of malignancy resulted from a tumour secreting PTH. Once a reliable assay for measuring circulating PTH was developed by Berson and Yalow,¹ it became apparent that the agent was PTH-like but not PTH itself. Parathyroid hormone-related protein (PTHrP) was discovered in 1987, in the search for the causative agent of humoral hypercalcaemia of malignancy.

PTH VERSUS PTHrP

PTH is the major hypercalcaemic hormone in mammals, but it has a very restricted localisation, being found only in the parathyroid glands. This hormone has a single action, raising circulating calcium when the parathyroid glands sense that levels are decreasing. In contrast, PTHrP is found in every organ and has local functions, including those in cell growth and differentiation, development, control of fetal calcium and smooth muscle relaxation, as well as its role as a hypercalcaemic factor.

At the N-terminal of their peptide sequences, PTH and PTHrP are highly homologous, with 8 of the first 13 amino acids being identical. This results in the two proteins being able to bind a common receptor known as the PTH1R. But that is where the similarity ends. PTH is a much shorter protein, and PTHrP is not only longer but also contains a number of regions that have specific functions, such as one which directs its transport into the nucleus. The transcript of the PTHrP gene is thought to undergo processing resulting in three different proteins differing in length but all starting with a common sequence.

So while it was apparent that PTH was a true hypercalcaemic hormone, PTHrP was an 'onco-fetal' factor with local actions as well.

'Comparative endocrinology has rewritten both PTH and PTHrP's stories'

SEEKING ANCESTRAL TIES

Evidence for a relationship between the two proteins was strengthened by the fact that, in humans, the PTH gene is on the short arm of chromosome 11 while the PTHrP gene is on the short arm of chromosome 12. These two chromosomes are known to have arisen in an ancient gene duplication event and the short arms have a number of related gene pairs on them, including *KRAS* and *HRAS*.

This spurred a number of research groups to look at the comparative endocrinology of the two genes and the resultant proteins. The aim was to find an animal where PTHrP's roles were simpler, to assist with uncovering the original (and possibly single) ancestral role that PTHrP played. It was also thought that because PTHrP has a more complicated gene and protein, it might be the older of the two. This was reinforced by the fact that the first animals to possess a distinct parathyroid gland were amphibians, and so they were thought to be the first vertebrates to produce PTH.

UNCOVERING ANCIENT ORIGINS

Comparative endocrinology has rewritten both PTH and PTHrP's stories. First, the PTH gene and protein have been found in bony fish, and two copies of PTH have been found in the oldest living jawed vertebrate (elephant shark, *Callorhynchus milii*, pictured), which has a cartilaginous skeleton. The elephant shark is thought to represent the 'reference vertebrate genome', which has not undergone much alteration for the last 400 million years. This animal lives in very deep water (up to 200 metres) and has a small genome, reflecting very little pressure for evolutionary change.

The discovery of PTH in these lower vertebrates means that a parathyroid gland is not required for its production and that multiple organs can produce PTH. The localisation of PTH was found to be more widespread in elephant sharks than in mammals and resembled PTHrP's presence in a number of tissues. Interestingly, there was only one copy of the PTHrP gene and its protein localisation was similar to that seen in mammals. This suggests that PTHrP's roles are fundamental and that there is strong evolutionary pressure for these functions to be retained.

The two copies of the PTH gene in the elephant shark genome have not persisted in humans and this leads one to believe that one of the PTHs has a deleterious effect; nature is not thrifty and redundant genes are largely retained in most vertebrate genomes.



Elephant shark, *Callorhynchus milii* ©marinethemes.com/Kelvin Aitken

CLUES FROM INVERTEBRATES

Comparative endocrinology is helping to uncover these original roles. Genome sequencing in invertebrates has demonstrated the presence of PTH1R, but as yet the invertebrate homologues of PTH and PTHrP have not been identified. This fits with the theory that the receptors appear first in evolution and the ligands follow.

There is still a great deal to learn about PTHrP and PTH. It has been apparent that the more we learn about PTHrP, the less we realise we know about PTH. It has been assumed that PTH is just a classical hypercalcaemic hormone, and very little research has been carried out to explore whether it has other roles. Comparative endocrinology will allow the exploration of possible novel roles for both PTH and PTHrP.

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DEVELOP OR DIE: THE DUAL ROLE OF CRH IN NON-MAMMALS

WRITTEN BY BERT DE GROEF AND SYLVIA VH GROMMEN



Corticotrophin-releasing hormone (CRH) is well known for being the initiator of the stress response. Upon detection of a stressor, hypothalamic CRH stimulates the pituitary to release corticotrophin (ACTH). In turn, ACTH activates the adrenals to release the actual stress hormones, glucocorticoids, which help us deal with stressors by mobilising energy resources and directing energy away from systems that are not critical for immediate survival.



Western spadefoot toad, *Spea hammondi*

Studies with non-mammalian species, however, indicate that the role of hypothalamic CRH was originally broader than that, a concept nicely demonstrated in amphibian metamorphosis.

DUAL PURPOSE HORMONE

During the transition from a generally aquatic tadpole to a more terrestrial juvenile, amphibians undergo a series of morphological, physiological, biochemical and behavioural changes, largely orchestrated by thyroid hormones, often in concert with glucocorticoids. Treatment with substances that increase thyroid hormone levels can stimulate metamorphosis. Thyrotrophin (TSH), for example, is a pituitary hormone that causes the thyroid to release thyroid hormones; TSH treatment forces tadpoles to initiate metamorphosis. Attempts to stimulate metamorphosis with thyrotrophin-releasing hormone (TRH), however, proved futile. In mammals, hypothalamic TRH is responsible for TSH release. In tadpoles, on the other hand, it just didn't seem to work.

Surprisingly, ovine CRH was found to be very potent at stimulating TSH release from frog pituitaries. Soon it was demonstrated that CRH is also a TSH-releasing factor in reptilian, avian and fish species, indicating that the original action of CRH was both thyrotrophic (feeding into the thyroid system) and corticotrophic (feeding into the adrenal system), and that this dual role is retained in most extant vertebrates.

Studies in chicken and bullfrog have shed some light on how CRH acts as a TSH-releasing factor. The pituitary of these species expresses two types of CRH receptor. CRH-R1 is expressed only by the corticotrophin-producing cells, whereas CRH-R2 is almost exclusively found on the TSH-producing cells. Substances that specifically block the action of CRH-R2 are capable of abolishing the TSH-releasing effect of CRH, an effect not seen when CRH-R1 blockers are used.

EFFICIENCIES AND SYNERGIES

If thyroid hormones act in synergy with glucocorticoids during critical life stage transitions such as amphibian metamorphosis, a single neuropeptide controlling their release is a very efficient way of guaranteeing their simultaneous release. At the same time, the system allows for fine-tuning: because two different CRH receptors are involved, it is possible to up- or downregulate one without affecting the other, making CRH 'more thyrotrophic' or 'more corticotrophic', depending on the needs of the body.

Moreover, as CRH acts as the interpreter between environmental cues (stressors) and the individual's physiology (stress response), this system allows for developmental plasticity: an individual can 'adjust' its developmental rate to the environmental conditions. For example, decreasing tank water levels stimulate CRH release in tadpoles of the western spadefoot toad (pictured), leading to higher thyroid hormone and glucocorticoid levels and ultimately acceleration of metamorphosis. In the wild, this would permit the tadpoles to escape their drying pool and thus increase survival chances.

MAMMALIAN MYSTERY

Intriguingly, there isn't a single report of a TSH-releasing effect of CRH in mammals, and TSH-producing cells in rat pituitary do not express CRH receptors. Yet CRH seems to be involved in developmental plasticity in mammals. CRH of fetal and/or placental origin affects the timing of birth, and correlates with the risk of preterm birth and fetal growth restriction. However, thyroid hormone levels in premature infants are lower than those in the normal fetus at similar gestational ages, so CRH does not seem to release TSH at this developmental stage.

On the other hand, TSH adenomas have been found to express CRH-R2, tempting researchers to speculate that human TSH cells express CRH-R2 in normal circumstances. Based on the anti-proliferative effect of CRH in endometrial cancer cells, it was suggested that the presence of CRH receptors in tumours may be used as a target for long term CRH therapy. However, if CRH is/ was a TSH-releasing factor in humans, CRH therapy would stimulate the adenoma even further!

MORE QUESTIONS THAN ANSWERS?

Overall, the available evidence suggests that CRH lost its thyrotrophic role in mammals and only retained its corticotrophic action. The proximate and ultimate reasons for this are, however, far from clear.

Why did the mammalian TSH cells lose their CRH receptors? Did a major change occur in the gene promoter of the receptor, causing it to lose its TSH cell-specific expression? The gene structure of CRH-R2 did indeed change in the lineage of mammals, where an additional gene segment and alternative splicing events give two different forms of the receptor, rather than just one as seen in most non-mammalian species.

And how is CRH-R2 expression switched back on in human TSH adenomas? From an evolutionary point of view, was it beneficial for mammalian CRH to only be corticotrophic? Is the loss of its thyrotrophic activity perhaps somehow related to the evolution of viviparity?

Comparative endocrinologists still have quite a few questions to answer.

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ONE, TWO OR THREE: HOW MANY BINDING PROTEINS DO YOU NEED?



WRITTEN BY SAMANTHA J RICHARDSON

Have you ever wondered why we have three thyroid hormone (TH)-binding proteins in our blood? Albumin, thyroxine-binding globulin and transthyretin (formerly known as prealbumin) are each present at a different concentration in human blood and each has a different affinity for THs. I believe that the answer can be found in vertebrate evolution.



Tammar wallaby, *Macropus eugenii*

THs are involved in the regulation of growth and development of all vertebrates. They require iodine for their synthesis. Thyroxine (T₄) is the form of TH predominantly synthesised in the thyroid gland, and contains four iodine atoms. It is commonly referred to as the precursor form of TH, and is the main form found in blood. The active form of TH is tri-iodothyronine (T₃), which is the form that binds to the nuclear TH receptors that are transcription factors, regulating the transcription of specific genes involved in growth, development and regulation of metabolic rate (including endothermy). As its name suggests, T₃ contains three iodine atoms. T₃ is produced in modest amounts by the thyroid gland, but most is generated at its sites of action: in the cells requiring regulation of gene expression by THs.

T₃ is generated from T₄ by an enzyme that removes one of the iodine atoms, thereby activating the TH. The deiodinases are a family of enzymes that remove or add specific iodine atoms from THs to either activate or inactivate them. The main point here is that iodine atoms are crucial in TH biology. For all vertebrates, iodine must be sourced from the diet.

MOVING FROM WATER ONTO LAND

The earliest vertebrates were fish. The ocean has an abundant supply of iodine, so scavenging iodine for TH synthesis is not a problem for these animals. Furthermore, fish only have a single TH distributor protein in their blood: albumin.

Amphibians make the transition from aquatic to terrestrial life when they undergo metamorphosis. Prior to metamorphosis (e.g. as tadpoles), amphibians have only albumin as their TH distributor protein in blood. Metamorphosis is driven by THs and during this period transthyretin is present in addition to albumin. So these animals have an additional TH distributor during a time of increased demand for TH. Furthermore, transthyretin has higher affinity for THs than does albumin, and so its presence thereby significantly augments the TH distribution capacity. This profile also occurs in smolting fish (e.g. salmon) and at critical stages of TH-regulated growth in reptiles, marsupials and eutherian (placental) mammals.

BECOMING WARM-BLOODED

Birds and eutherian mammals are endothermic (warm-blooded). Thermoregulation by metabolic means is controlled (at least in part) by THs. Thus, endothermy can be seen as an increased requirement for THs, when compared with ectothermic (cold-blooded) animals. Birds and eutherians have both albumin and transthyretin as TH distributor

proteins in their blood throughout life. Some eutherians (e.g. humans) also have the third TH distributor protein, thyroxine-binding globulin, in their blood. Thyroxine-binding globulin has even higher affinity for THs than does transthyretin. Thus, we see an increase in the number of TH distributor proteins in the blood of vertebrates, not only correlated with the move out of water onto land, where the supply of iodine is not as abundant, but also with increased demands for TH, either transiently (e.g. in metamorphosis) or constantly (e.g. in endothermy). The affinity of thyroxine-binding globulin for THs is so high that it does not deliver a significant amount of TH to tissues, but acts more as a storage reservoir.

WHAT THE AUSTRALIAN MARSUPIALS REVEALED

The Australian marsupials are interesting to consider at this point. One classification system divides them into two groups: Polyprotodontia and Diprotodontia. Polyprotodont marsupials are more closely related to the ancestral American marsupials, which were all polyprotodonts, and from which diprotodonts diverged.

In general, the polyprotodonts are carnivores (e.g. Tasmanian devils) and the diprotodonts are herbivores (e.g. kangaroos). Herbivores have significantly longer digestive tracts than carnivores and, because THs are very fat soluble, longer digestive tracts could be 'sinks' for THs to partition into and thus be removed from circulating in the blood. However, whereas polyprotodont marsupials only have albumin as a TH distributor protein in blood, diprotodont marsupials have both albumin and transthyretin.

Intriguingly, marsupials are considered 'poor endotherms', i.e. they are not as good at maintaining their body temperature as true endotherms, and yet this is a group of animals where we see the transition from a single TH distributor protein (albumin) to the combination of albumin plus transthyretin.

AN EVOLVING NEED

So, during vertebrate evolution there has been a change from one to two to three TH distributor proteins in the blood. Each change can be correlated with a physiological selection pressure, and, in my opinion, explains why humans have albumin, transthyretin and thyroxine-binding globulin in their blood.

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ENTER THE THYROID HORMONES! LESSONS FROM EVOLUTION

Thyroid hormones (THs) are key players in regulating development of the brain. Insufficient THs during human prenatal development can lead to cretinism and mental retardation. Insufficient THs in adult life can result in clinical depression. THs act by regulating transcription of specific genes, including those involved in myelination of nerve axons. Thus, it is crucial that sufficient THs move from the blood into the brain at critical stages of development.

THE BLOOD-CEREBROSPINAL FLUID BARRIER

The choroid plexus is located in the ventricles of the brain and forms the blood-cerebrospinal fluid (CSF) barrier. In reptiles, birds and mammals, the major protein synthesised and secreted by the choroid plexus is transthyretin, a protein that binds and distributes THs. This transthyretin is secreted into the CSF and is involved in the movement of THs from the blood into the CSF. The onset of transthyretin synthesis in the choroid plexus is thought to have occurred about 300 million years ago in the stem-reptiles, whose brains showed the first traces of neocortex.

The choroid plexus develops more quickly than other parts of the brain and has a major role in controlling CSF composition. The brains of precocial animals (e.g. chickens and sheep) are well developed at birth, as the stage of rapid brain growth is prior to birth. In contrast, the brains of altricial animals (e.g. rats and mice) are less well developed at birth, as their period of rapid brain growth is postnatal. However, for both groups of animals, the maximal transthyretin production in the choroid plexus is just prior to the period of rapid brain growth, which requires THs. Thus, transthyretin synthesis by the choroid plexus appears to have a significant role in moving THs from the blood into the brain.

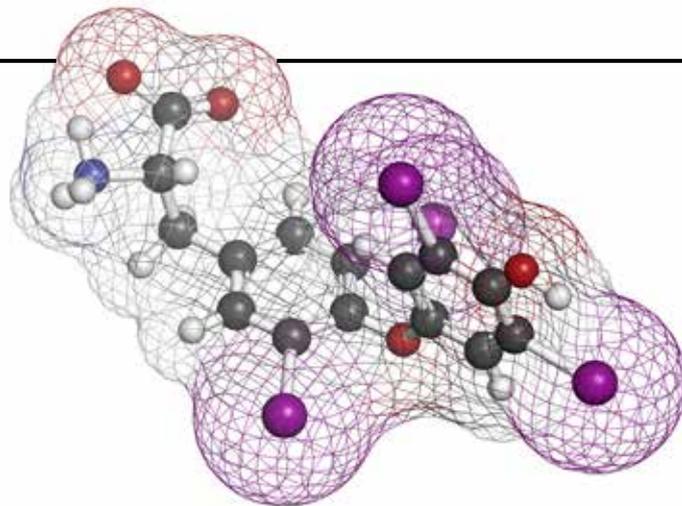
'The amino acid sequences and 3D structures of transthyretins have been extremely highly conserved ... the 3D structure of transthyretin-like protein from Salmonella can be superimposed over that of human transthyretin!'

MAMMALS: THE EXCEPTION NOT THE RULE

In all species of fish, amphibians, reptiles and birds that have been studied, transthyretin preferentially binds the active form of thyroid hormone (tri-iodothyronine, T3), whereas in mammals transthyretin preferentially binds the precursor form of thyroid hormone (thyroxine, T4). Thus, mammals are the exception in this regard. Is it possible that transthyretin made by the choroid plexus of mammals moves T4 into the brain whereas in other animals transthyretin moves T3 into the brain?

STRUCTURAL CHANGES

The amino acid sequences and 3D structures of transthyretins have been extremely highly conserved during evolution (e.g. the 3D structure of transthyretin-like protein from *Salmonella* can be superimposed over that of human transthyretin!). Intriguingly, the amino acids in the TH-binding sites of all transthyretins are identical, which does not explain the differences in affinities for T3 versus T4.



Chemical structure of thyroxine molecule

The region of greatest variation during evolution of transthyretin has been the first 9–12 amino acids of the proteins, which move like arms around the entrances to the channel containing the TH-binding sites. Transthyretins with longer, more hydrophobic 'arms' have higher affinity for T3 (fish, amphibians, reptiles), whereas transthyretins with shorter, more hydrophilic 'arms' have higher affinity for T4 (mammals). We elucidated the molecular mechanism for shortening the 'arms', which was due to a series of single step-by-step changes in the DNA.

INCREASING CONTROL

What was the selection pressure for the change to transthyretin from distributing T3 to distributing T4? A greater level of control! The receptors for THs are transcription factors that regulate expression of specific genes, in particular those involved in development and maturation of the central nervous system. Distributing T3 (the active form of TH) around the body and CSF is analogous to distributing a loaded gun. However, if the unloaded gun was distributed (i.e. the inactive form, T4), this would be much safer, requiring an additional level of regulation in order for it to be fired.

THs enter cells via membrane-bound TH transporters or by diffusion. Inside the cell, activation and inactivation of THs are controlled by a family of enzymes called deiodinases. Some are involved in TH activation (e.g. conversion of T4 to T3) and others are involved in inactivation (e.g. conversion of T3 and T4 to inactive forms). Each of the deiodinase family members is expressed in a tightly regulated spatial and temporal manner, especially in the brain. Thus, as mammalian transthyretins distribute the precursor form of TH in blood and CSF, a greater level of regulation is presumably required at the level of deiodinases and/or TH transporters for TH action in mammals compared with other vertebrates. This is particularly important in the brain.

IN CONCLUSION

Transthyretin is one of three proteins in human blood that binds and distributes THs, yet it is the only TH distributor protein synthesised in the brain. Individuals lacking either of the other two proteins are healthy. However, a human being lacking transthyretin has not yet been described – perhaps due to the crucial role it plays.

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DOES FELINE HYPERTHYROIDISM DAMAGE THE KIDNEY?

WRITTEN BY TIM WILLIAMS



Cats are the only companion animal species in which hyperthyroidism occurs naturally and with relative frequency, which makes them an interesting model for human disease. Hyperthyroidism in cats, which has pathological similarities to toxic nodular goitre in humans, is the most commonly diagnosed feline endocrinopathy, and is reported to affect more than 5% of all cats over the age of 9 years.¹

The prevalence of hyperthyroidism has been increasing since the late 1970s, when the condition was first reported, but the reason remains unknown. Case control studies have identified an association with the feeding of wet food (particularly from so called 'pop top' or easy open cans).² The wide variation in the iodine content of cat food might be important, but no clear causal relationship has yet been elucidated.

Although some genetic studies to uncover somatic mutations in the thyroid gland of affected individuals have been performed, and some mutations have been identified, further work to determine the functional significance of these changes in cats is needed.

IMPACT ON THE KIDNEYS

Hyperthyroid cats tend to be old (usually over 10 years) and often present with multiple co-morbidities including chronic kidney disease (CKD) and systolic hypertension. The prevalence of these co-morbidities, particularly CKD, appears to be higher than we would expect in older cats in general, since up to 50% of hyperthyroid cats had concurrent CKD in some studies.³ This led to our hypothesis that hyperthyroidism might be damaging to the kidney.

The effect of hyperthyroidism on glomerular filtration rate (GFR) has been extensively studied in both human and feline patients, demonstrating that hyperthyroidism increases GFR, while restoration of euthyroidism normalises GFR.^{3,4} Longer term follow up of renal function in human hyperthyroidism has not been reported, so it is not known if these patients are at increased risk of developing CKD following treatment. It is possible that renal damage might occur in human patients, but that it might remain subclinical as many present with hyperthyroidism in middle age when they are at a lower risk of developing concurrent CKD. If hyperthyroidism was found to be damaging to the kidney in cats, then further investigation of the consequences of hyperthyroidism on renal function in human patients over the longer term might be of benefit.

Since thyroid hormones have a broad range of actions, the systemic effects of hyperthyroidism are widespread. Hyperthyroid cats are proteinuric, have increased activation of the renin-angiotensin-aldosterone system (RAAS), and have altered calcium and phosphate homeostasis, including hyperphosphataemia and hyperparathyroidism. All of these pathophysiological changes are postulated to be damaging to the kidney in both cats and humans, and therefore could all be pathophysiological mechanisms for renal damage in hyperthyroidism.

TESTING THE HYPOTHESIS

We have assessed whether hyperthyroidism might damage the feline kidney by examining the relationship between the presence and severity of proteinuria, RAAS activation, hyperphosphataemia and hyperparathyroidism and the presence of concurrent CKD in client-owned hyperthyroid cats.⁵⁻⁸ The clinical data accumulated to date have not demonstrated a significant association between these pathophysiological changes and the presence of CKD, which suggests that hyperthyroidism may not cause renal damage. However, these studies did uncover some interesting pathophysiological differences between humans and cats with hyperthyroidism.



Calcium and phosphate handling appears to be profoundly altered in both human and feline patients with hyperthyroidism, though the pattern of these changes is markedly different. The most striking anomaly appears to be the relative differences in serum calcium, with hyperthyroid cats being relatively hypocalcaemic, whereas hyperthyroid human patients (whether with Graves' disease or toxic nodular goitre) are relatively hypercalcaemic.^{9,10} We have shown that thyroid hormone itself could have a direct effect on calcium regulation which is independent of control by other calcium regulatory hormones such as parathyroid hormone and calcitriol. Clearly there are species differences in the effects of excess thyroid hormone on the body, which are worthy of note when conducting animal-based studies of human diseases like hyperthyroidism.

Without doubt, hyperthyroidism does have profound effects on renal function, which are reversed following treatment. However the results of clinical studies in client-owned cats with naturally occurring hyperthyroidism do not support the hypothesis that hyperthyroidism is damaging to the kidney. CKD and hyperthyroidism in old cats are therefore probably co-morbid diseases, which do not influence the pathogenesis or progression of one other.

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Tim completed a PhD on the interaction between thyroid disease and renal function at the Royal Veterinary College, London, in 2012. His research focuses on the pathophysiology of hyperthyroidism in cats, and the evaluation of novel urinary biomarkers for the diagnosis of feline chronic kidney disease.

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OBESITY IN DOGS: A BIG PROBLEM

WRITTEN BY ELEANOR RAFFAN

'I am inclined to resent the wide publicity recently bestowed upon a certain [cat which] has achieved notoriety by measuring 33 inches round the waist and weighing just over 2 stone. That is a good deal of cat; about three times too much, to be perfectly frank.'

'Far be it from me to sneer; obesity, whether in beasts or baronets is a matter for pity, not for mirth. When I look at what is styled as a "pet dog", wheezy and corpulent, his capricious appetite tempted with dainty food, his healthy canine instincts destroyed by wicked or unnatural pampering, I wonder that its owner is not ashamed.'



Labradors were initially bred as retrieving dogs, but today are popular family pets. They are commonly obese and have a reputation for being extremely motivated by food. (Oil painting ©The Kennel Club/Rosamund Oldfield.)

Not my words, but those of a certain KRG Browne writing in the *Daily Mail* in 1934, and secondly 'A lady', so upset about pampered pooches she wrote to the *Nottingham Post* in 1881. Not much has changed; there has been much publicity about pet and human obesity over recent years. But does the reality match the hype?

For the first time in human history, there are more overweight and obese people on the planet than people suffering from malnutrition. Given the high burden of obesity-related disease in humans, it's no wonder human obesity is big news.

IS OBESITY SUCH A BIG DEAL IN COMPANION ANIMALS?

Estimates suggest at least a third of adult dogs and cats are overweight. Obese dogs die sooner and have a higher incidence of orthopaedic, cardiac, respiratory, urinary, reproductive and dermatological disorders, as well as of some cancers and anaesthetic complications. In cats, the health risks of obesity are also well established; diabetes, hepatic lipidosis, urinary tract disease, lameness and dermatopathies predominate. As such, there is little doubt obesity represents a significant health and welfare problem for pet dogs and cats.

Although there is much overlap of obesity-associated disease between dogs, cats and humans, there are also notable differences. For instance, feline diabetes is predominantly a consequence of obesity-related insulin resistance, as in humans. That contrasts with the picture in dogs where, although there is mounting evidence that obesity is associated with insulin resistance, the links between obesity and diabetes are not well established.

Perhaps the most striking interspecies difference relates to cardiovascular disease. Atherosclerosis and stroke, which are such common sequelae to human obesity, are almost unheard of in veterinary species, despite the fact that insulin resistance, hyperglycaemia and dyslipidaemia occur in obese dogs and cats. It is not clear whether this reflects a fundamental resistance to atherosclerosis, or is simply because they don't live with obesity for so many years, meaning vascular lesions don't have time to develop.

Other comparisons ripe for further investigation include the parallels between feline hepatic lipidosis and human non-alcoholic fatty liver disease, and the reason why dogs don't develop obesity-associated diabetes.

INDULGENT OWNERS OR HARD WIRED BIOLOGY?

With calorie-dense food increasingly affordable and sedentary lifestyles more common – for both humans and pets – it is no surprise that obesity is increasing. But dismissing human or animal obesity as a straightforward consequence of gluttony and laziness doesn't hold up to scrutiny under the spotlight shone by mounting evidence that appetite and energy expenditure are closely regulated homeostatic mechanisms, subject to influence by genetic and environmental factors.

Obesity is highly heritable in humans and strong breed predispositions suggest genetics are equally important in dogs. Labradors regularly top the obesity tables. Are we really to believe Labrador owners are so much more exercise-averse and indulgent with food that their dogs develop obesity, while owners of borzois and pointers (both commonly lean breeds) are a virtuous bunch who carefully regulate their dogs' weight? No – it is far more plausible that the tendency to eat to excess is hard wired in Labrador biology.

GOdogs!

It was to investigate this that I set up the GOdogs project, collecting a cohort of Labradors to study the genetics of obesity and appetite in the breed. If you are a Labrador fan, do you know any overweight, highly food-motivated Labradors or – and these are the dogs which are particularly hard to track down – lean Labradors who are not highly food-motivated? If so, please do get in touch via www.GOdogs.org.uk. Participating dogs donate a saliva sample and must be weighed and condition-scored by a vet or vet nurse. Exciting preliminary findings suggest that a mutation in a gene known to be important in human appetite regulation is a major modifier of appetite and obesity in Labradors – keep your eyes out for future results!

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STRESS AND LIFE: LESSONS FROM COMPARATIVE MODELS

WRITTEN BY BRONWYN M MCALLAN

In the developed world, modern life is considered by many as 'stressful'. Such a statement is regarded as contentious by some stress physiologists. In the last 100 years, these same parts of the world's population have seen the infant mortality rate plummet and post-partum maternal death rates become negligible (WHO data 2014). These are considered major stressful life events and our exposure to them is declining in modern society.

Coupled with the increase in life expectancy, one would expect the perception of stress in society to have decreased. However, this does not appear to be the case, and as the discoverer of the stress hormones, the glucocorticoids (cortisol and corticosterone), Hans Selye (1907–1982) stated, 'stress is life and life is stress'.

DEFINING STRESS

Selye's pioneering work on the biology of the stress response gave us the origins of research into the identity of the glucocorticoids, the neuroendocrine axis of the stress response and the definition of 'stress' and 'stressor'. These terms are now widely used in the scientific literature and by the wider public and, unusually, they have the same meanings in both domains.

'Stress' is the physiological cascade promoted by the stimulation of the sympathetic nervous system's release of the catecholamines and subsequent upregulation of the release of glucocorticoids. The pounding of the heart, raised blood pressure and increased metabolism are all physical experiences described by a stressed person. A 'stressor' is anything that promotes the stress response, and this really can mean anything: cold, heat, hunger, thirst and psychological stressors such as the threat of job loss, abuse or war. Moreover, as recognised by Selye, one person's 'eustress' (positive stimulation or good stress) is another person's 'distress'.

THE VALUE OF ANIMAL MODELS

Interestingly, although medically trained, Selye was not a practising clinician but worked in experimental medicine throughout his life, mostly on laboratory animals. Indeed, the backbone of the work on understanding the stress response is performed on non-human mammals.

How important are animal models for our understanding of stress? Discovery of the basic mechanisms of the stress neuroendocrine axis (hypothalamus-pituitary-adrenal cortex) was made using animal models, as was elucidation of the physiological actions of the glucocorticoid hormone cortisol. The promotion of gluconeogenesis, glycogenolysis, proteolysis and lipolysis by cortisol (or corticosterone, depending on the animal) were all initially observed in animal models.

Moreover, discovering that cortisol promotes breakdown of proteins and fats explains some of the symptoms seen in chronically stressed individuals. Why can't a person gain muscle mass no matter how much they eat and exercise? Cortisol prevents the uptake of glucose into most cells except for those in the brain and liver, and the formation of new glucose is used for continued function of these organs in order to maintain survival. Chronically raised cortisol is known to promote insulin resistance and central adiposity, similar to Cushing's syndrome. Besides humans, these symptoms have been seen in creatures as diverse as the carnivorous marsupial *Antechinus* and an array of captive zoo animals.

OUTCOMES OF STRESS

Finding that cortisol does not just promote the formation of new glucose, but also affects other physiological systems, has had profound effects for understanding some of the outcomes of chronic stress. Besides the complexity of insulin resistance and metabolic disruption, the role of glucocorticoids in post-traumatic stress disorder (PTSD) and in dysregulated immunity has been well documented in non-human animals.



The author with an echidna, a monotreme from Australia that lays eggs but makes milk. Due to its unique evolutionary history, echidnas are often studied in comparative research.

One of the paradoxical outcomes of chronic stress is suppressed immunity. Work on animals from fish to non-human primates has demonstrated that cortisol has a wide range of specific effects on the immune system. These include upregulation of sympathetic innervation of the lymph nodes, promoting apoptosis of thymocytes and lymphocytes, suppressing leucocyte trafficking (surveillance by leucocytes and their movement out of the bloodstream), disruption of antigen presentation to cytotoxic T lymphocytes and upregulation of proinflammatory cytokines.

The suppression of immunity when an individual is stressed seems counter-intuitive, as one would expect that a stressed individual should be ready for all eventualities, rather than risk compromise by pathogenic challenge. Why this should be so is best known from fish, where, when exposed to cortisol in the short term, a 'sculpted' immune system allows the fish to respond successfully, and metabolically cheaply, to pathogens. It is the long term exposure to a stressor that promotes the failure of immunity, seen in humans as inappropriate autoimmune responses, or the inability to recover from viral or bacterial infections.

The suppression of immunity during stress is not the only paradox for stress researchers and clinicians. PTSD is one of the most complicated and perplexing conditions in humans, and here animal models are helping us to understand the mechanisms. Tree shrews exposed to social stress display many of the same symptoms, including the endocrine, physiological and mood changes. Importantly, the hippocampal disruption in the brain, including dendritic changes and volume shrinkage, which has been implicated in PTSD, was first described in these 'stem primates'. Complex investigations into social stress, and the implications of early childhood stress for PTSD, have drawn on data from tree shrews and non-human primates.

Our understanding of the complex interactions between the stress response and long term survival owes much to Hans Selye's pioneering work, and also to the animals providing the insights into stress physiology.

BRONWYN M MCALLAN
School of Medical Sciences,
University of Sydney, Australia



STUCK IN THE MIDDLE

FROM OUR SCIENCE COMMITTEE CORRESPONDENT

Two very different papers caught my eye this week, both in high impact journals, and both with data and content indicating groups at the top of their respective games.

I came across these papers because I wanted to find out more about two people I had met at a hotel breakfast table whilst at a conference. Both scientists were in their early 30s, similarly educated and trained. Although both were interested in metabolic disease, one had chosen to concentrate on *in vivo* models, while the other had a passion for human genetic studies. It's difficult to make a complete judgement of someone's intellectual and technical prowess based on their choice of frosted cereal and how they tackle a pot of Tiptree jam, but, on the face of it, here were two sane, competent people who had chosen to try and make a go of it in science.

However, if the results of my PubMed search were the measure, my two breakfast companions could be judged to be poles apart. The chap working on animal models was the first of just three authors on his paper, while the geneticist was 78th in a cast list of 114.

On the face of it, the author list should be a point of order, a mechanical exercise registering the relative efforts of contributors. So, she had the idea and funded it, he spent the last 6 months in the lab doing the work,

they helped out intermittently: last, first and middle authors respectively. Through this system, one can signal to the granting bodies that you are worthy of further backing and have the mettle to prosecute a worthwhile project through to conclusion. Keep going and fellowship and grants will lead to positions and tenure.

What, then, of those affected by 'middle author syndrome' (or simply a footnote in the acknowledgements)? Is there a way to meaningfully compare efforts, with 30 middle author papers adding up to one first? Is it possible to continue to plug away in such a role, forever the 'domestique' in the scientific peloton? It is one thing to push hard for the team win, but it takes a degree of personal equipoise to work hard in the shadows all your professional life, while watching the plaudits focus on another individual at the top of the author list.

Any meritocratic system needs a way to judge ability and requires metrics to function. This is right and proper. One hopes that 'good will always out', with talent and drive finding a way through. However, how to do this whilst supporting unsung colleagues that so crucially shape the working landscape remains a challenge.

TONY COLL
Science Committee correspondent

A CAREER IN ENDOCRINOLOGY: WHAT THE SOCIETY CAN DO FOR YOU

FROM OUR CAREERS CORRESPONDENT

The Society for Endocrinology is dedicated to providing support for you, our members, at every stage of your career. With a wide range of events and a vast programme of grants and awards, we aim to equip you with the tools you need to take control of your future. From the Career Development Workshops, aimed at supporting our clinical and basic science researchers through career hurdles, to Clinical Department Visit Grants, allowing clinicians to work at state of the art clinics in the UK or even abroad, we support members throughout their careers.

CAREERS FAIRS AROUND THE COUNTRY

In recent months, we have begun to review and reinvigorate our careers programme to attract and retain members so they can enjoy a bright career in endocrinology. Our education leads at each medical school in the UK have been working to ensure that medical students and undifferentiated trainees are inspired to join the specialty by giving them the opportunity to take up free places at a series of Society events. We are also encouraging more bioscience graduates to enter into a multitude of bioscience careers, including endocrinology, by running a series of Life Sciences Careers Conferences, in collaboration with the Society of Biology.

CAREERS RESOURCES

The Society's newly produced specialty booklet, written by members, shows how exciting and diverse a career in endocrinology and diabetes can be. The booklet can be downloaded from the Society Careers homepage and will be available at the upcoming medical careers fairs the Society will be attending.

For our basic scientist members, the Society is working in collaboration with the Society of Biology and other learned bodies on a series of careers activities and training opportunities for prospective undergraduates all the way through to postdoctoral researchers. We are reviewing our 'Next Steps: options after a bioscience degree' careers booklet, which provides advice for students and recent graduates on the options open to them, while helping them to plan their careers. The guide can be downloaded from the Society website at <http://bit.ly/pb0GpD>.

As part of our ongoing careers support, we will be further developing our online careers resources and would be pleased to hear your suggestions or feedback at kate.bowman@endocrinology.org. Keep up to date at www.endocrinology.org/careers.



KATE BOWMAN
Professional Affairs Officer,
Society for Endocrinology

UPCOMING CAREERS FAIRS - DATES FOR YOUR DIARIES

Life Science Careers Conferences
(<https://events.societyofbiology.org/LSCC>)

📅 15 OCTOBER 2014, UNIVERSITY OF LIVERPOOL

📅 22 OCTOBER 2014, ROYAL VETERINARY COLLEGE (LONDON)

📅 29 OCTOBER 2014, STAFFORDSHIRE UNIVERSITY

Royal College of Physicians Medical Careers Day
(<http://rcplondon.ac.uk/medical-careers-day>)

📅 20 SEPTEMBER 2014, RCP, LONDON

BMJ Careers Fair
(<http://careersfair.bmj.com/en/1/national.html>)

📅 17-18 OCTOBER 2014, BUSINESS DESIGN CENTRE, LONDON



SCIENCE AND PUBLIC TRUST: A YOUNG ENDOCRINOLOGIST IN PARLIAMENT

Parliamentary Links Day is organised annually by the Society of Biology together with the Society for Endocrinology to improve the relationship between the science and engineering community and parliament. It brings together representatives from the two groups to discuss key issues, including this year's topic: 'Science and public trust'.

The day began with an entertaining welcome from the Speaker of the House of Commons, the Rt Hon John Bercow MP, in which he declared his regret at never pursuing his scientific interests, and paid tribute to the scientific passion of the late Tony Benn. Other MPs addressing the audience included Chair of the Science and Technology Select Committee Andrew Miller MP, Shadow Minister for Universities, Science and Skills Rt Hon Liam Byrne MP and Science and Technology Select Committee Member Stephen Metcalfe MP. The MPs were keen to engage more with scientists, but noted that decisions made by parliament on scientific issues need public support.

Representing the science and engineering community were Government Chief Scientific Adviser Sir Mark Walport and Nobel Prize Winner and President of the Royal Society Sir Paul Nurse. Sir Paul Nurse summarised the concerns of the community perfectly by saying, 'Good science is built on honesty and openness and consideration of all the evidence' and 'Scientific knowledge is often provisional, but children are taught that science is written in stone'.

The panel discussions were the day's main focus. Two panels consisting of science journalists, academics and scientific organisations debated the topics of establishing trust in science and engaging with the public/parliament. Important issues included use of social media, increased questioning of data by the public, consistent public engagement, greater transparency and how to inspire younger generations.

The day was filled with passionate discussions and gave an opportunity for scientists from different disciplines to communicate common issues. Where else could a molecular biologist converse with an engineer who helped design the London Shard? Overall, it is apparent that more scientists/engineers are needed in parliament but, failing that, if our community isn't happy with the way parliament deals with scientific issues, then we must stand up and say so.

KATE LINES
Young Endocrinologists' Steering Group

You can find out more about Parliamentary Links Day at <http://bit.ly/1opeOw8>.



Sir Paul Nurse, President of the Royal Society, speaks at Parliamentary Links Day



REGIONAL

REGIONAL CLINICAL CASES

FRIDAY 5 DECEMBER 2014

CROWNE PLAZA BIRMINGHAM NEC HOTEL, BIRMINGHAM
IN ASSOCIATION WITH THE MIDLANDS ENDOCRINE CLUB

The Regional Clinical Cases Meeting provides an indispensable forum for the exploration and discussion of interesting and notable cases from the last year.

Alongside showcasing ten oral communications chosen from the highest-scoring abstracts, the meeting offers a variety of lectures delivered by leading endocrinologists.

The Society for Endocrinology's Clinical Cases Meetings provide an ideal forum for trainees to present cases to peers and senior colleagues.

Find out more and submit your case online at www.endocrinology.org/meetings/clinicalcases before the 6 October 2014!



LENDING YOU A HAND: SOCIETY SUPPORT FOR EDUCATION AND TRAINING

WRITTEN BY WIEBKE ARLT AND KAREN CHAPMAN



Your Society's ambition is to be a world-leading authority on hormones. To reach this goal, we on the Clinical and Science Committees are focusing our activities in key areas to help you and your fellow members.

One of the Society's strategic priorities is to attract medical students and undifferentiated trainees into the specialty of endocrinology and diabetes. Another is to provide forums for basic scientists to share the latest thinking and form collaborations to advance research in endocrinology. Underpinning these priorities is a commitment to support you, as endocrinologists, at every stage of your career.

We are currently working on a number of initiatives in these priority areas, co-ordinated by Dr Maja Lubczanska at the Society's Bristol office. These span clinical and scientific areas of endocrinology, many covering both aspects, as shown below.

WIEBKE ARLT
Chair, Society Committee

KAREN CHAPMAN
Chair, Society Committee

CLINICAL INITIATIVES

Attending high-profile careers fairs organised by the BMJ and RCP* that attract many unspecialised trainee doctors and medical students

Using online resources to support learning for endocrinology and diabetes trainees

Promoting sources of funding for medical students, e.g. the 5-year, UK-wide INSPIRE scheme, co-ordinated by the Academy of Medical Sciences and supported by the Wellcome Trust. Several Society members are INSPIRE leads in their institutions

Assessing the feasibility of supporting structured endocrinology department visits for medical trainees

Producing resources to illustrate the career pathways in endocrinology and the breadth of specialist areas

Strengthening links with organisations with similar goals, e.g.:

- the Academy of Medical Sciences, which has a well-established one-to-one mentoring scheme
- the Society of Biology, which co-ordinates work between learned societies

Including career development sessions for students, trainees and early career professionals at our annual conference, in liaison with the Society's Programme Committee

Recruiting student ambassadors at each university/medical school to deliver 'endocrinology clubs' with the support of Society medical leads and the office team

SCIENCE INITIATIVES

Assessing the feasibility of hosting cutting edge subject-focused science meetings at international venues, featuring leading experts

Examining provision of resources to create Endocrinology Basic Science Research Networks, to improve collaboration and help identify mentors in different institutions

Research joint membership with other major learned societies

*BMJ, *British Medical Journal*;
RCP, Royal College of Physicians.

If you have any comments or suggestions, or would like to get involved, please email maja.lubczanska@endocrinology.org.

IMPRESSIVE IMPACT FACTORS!

The Society for Endocrinology is delighted to announce impressive 2013 impact factors for all its journals.



Endocrine-Related Cancer has received a strong impact factor of 4.907, and remains in the top quartile of the 'oncology' and 'endocrinology and metabolism' categories.



Journal of Endocrinology's impact factor of 3.586 is the second highest it has ever achieved.



Journal of Molecular Endocrinology's impact factor has risen to 3.621.



Clinical Endocrinology continues to stand strong, with an impact factor of 3.353.

We thank all the authors, reviewers, readers and editorial boards who have ensured that our journals continue to make a significant contribution to the global scientific and medical communities.

SOCIETY JOURNALS OFFER NEW SERVICE FOR AUTHORS



We are delighted to announce that all Society for Endocrinology journals published by Bioscientifica will be piloting a new article-sharing service for authors: Kudos. Designed to help authors maximise the visibility and impact of their research, Kudos helps authors to use social media effectively to engage readers. Authors can create 'profiles' for their published articles, add lay summaries, and include impact statements, to increase the online exposure of their work. In the testing phase of Kudos, articles shared via this platform across a range of publishers had 19% more daily downloads than articles not shared. We hope that you will find Kudos valuable, as authors, readers, and Society members.

NOW IN PUBMED!

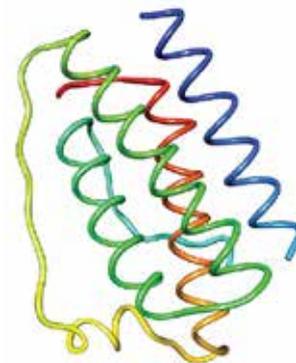


Endocrinology,
Diabetes & Metabolism
CASE REPORTS

Endocrinology, Diabetes & Metabolism Case Reports is now indexed in PubMed. Society for Endocrinology members receive a 20% discount on the article publication charge. To find out more, visit www.edmcasereports.com.

JOURNAL OF ENDOCRINOLOGY CELEBRATES LEPTIN ANNIVERSARY

In 1994, Jeffrey M Friedman demonstrated isolation of the *ob* gene by positional cloning, and identified its product, leptin. This seminal discovery revealed that fat is an endocrine organ. To celebrate the 20th anniversary of Friedman's breakthrough, *Journal of Endocrinology* will be publishing a special issue on leptin, guest-edited by Professor Sir Stephen O'Rahilly, President of the Society for Endocrinology, and a leading contributor to the leptin research field. The issue will be published in autumn 2014 and will feature an overview from Friedman, a series of reviews covering all aspects of leptin biology and original research papers on the subject. Members of the Society can read *Journal of Endocrinology* free of charge at www.biosocialalliance.org.



X-ray crystallographic structure of human leptin W100E (PDB ID:1AX8), shown as cartoon with rainbow colour scheme. From: Peelman *et al.* <http://dx.doi.org/10.1530/JOE-14-0264>.



Our leading journal linking hormones and cancer, *Endocrine-Related Cancer*, is now on Twitter. Follow us at @EndoCancer

IN THE PUBLIC ARENA: SEX, DIABETES AND CANCER

WRITTEN BY OMAR JAMSHED



Why do we fall in love? What is the true cost of surviving cancer? How do we approach the immense challenge posed by type 2 diabetes? Few questions were left unanswered at three of the Society's recent public engagement events, thanks to contributions from some of the Society's biggest thinkers.

They shape our mood and sexual behaviour, but are we really just slaves to our hormones? Speaking to a packed room of 150 people at *The Times* Cheltenham Science Festival, psychologist Viren Swami, consultant Helen Simpson and endocrinologist Gareth Leng discussed lust, love and sex. Using recent evidence, Dr Swami suggested that hungry men are more likely to be attracted to larger, more voluptuous women – a correlation Professor Leng linked to the fact that sex and hunger are two fundamental drives controlled by the same part of the brain. Some say beauty and folly are general companions but it looks like the stomach plays a role too. And no one had a bigger appetite for the story than journalists, who wrote extensively about our event in *The Daily Mail*, *The Telegraph*, *The Independent* and *The Mirror*. A truly satiating experience for all!

In 2030, four million Britons will be living with cancer, hundreds of thousands of whom will have long term health problems. This was the sobering introduction to our second event at *The Times* Cheltenham Science Festival. Macmillan Cancer Support's Chief Medical Officer Jane Maher, consultant endocrinologist Robert Murray and Macmillan consultant nurse Diana Greenfield discussed the problems the medical profession face in helping cancer survivors. Despite being battered by the weather, our outdoor venue was fully sold-out – a strong indicator of the public's appetite to tackle difficult issues.

'It was great to see so many of our researchers interacting with the public and for the public to see their passion for diabetes and endocrine research,' said Dr Matthew Simmonds.

By 2020, 7.2% of Oxfordshire will be living with diabetes. Research teams at the Oxford Centre for Diabetes, Endocrinology and Metabolism hosted 'Unravelling the mysteries of diabetes', a 4-hour public event showcasing diabetes and endocrinology research. The Society-funded event allowed 200 members of the public to learn all about Dexa scanners and how they can be used to tell if abdominal fat is pushing up the pancreas, as well as the latest technologies to help diabetics efficiently, such as a video-link service for doctors to diagnose patients at risk of hypoglycaemia. They also played with a prototype breath-analyser that may one day test for ketoacidosis without the need for blood finger pricks.

OMAR JAMSHED
Communications Assistant, Society for Endocrinology

SOCIETY GRANT SUPPORTS THYROID FAMILY CONFERENCE

WRITTEN BY JULIA PRIESTLEY & TIM CHEETHAM



With the support of a Public Engagement Grant from the Society for Endocrinology, the British Thyroid Foundation (BTF) hosted a 1-day conference for families of children with thyroid disorders, to enable them to learn about thyroid disease and meet others in the same position. The event, the first of its kind in the UK, took place in Leeds and was attended by over 25 families from across the UK as well as Ireland and France.

The BTF thanks the paediatric endocrine team from Leeds General Infirmary (LGI) who gave presentations, led workshops and answered questions throughout the day. There were also talks from parents and hugely reassuring presentations by two teenage girls who had been diagnosed with congenital hypothyroidism (CHT) and had clearly grown up into bright, articulate young women. Younger children took part in activities to help them understand more about their thyroid and the importance of taking their medication and having regular blood tests.

The BTF, with the help of the team from LGI, will now produce a short leaflet that can be given to families at the time of diagnosis of CHT. This grant was, in our opinion, an extremely productive use of Society funds.

JULIA PRIESTLEY
British Thyroid Foundation

TIM CHEETHAM
University of Newcastle

THE EARLY CAREER GRANT OR WHY I REALLY LOVE OUR SOCIETY

WRITTEN BY JON W MUELLER



What has the Society for Endocrinology done for me to inspire a title like that? Let me start by telling you a little of my background.

I first encountered hormones while studying biochemistry at the University of Halle-Wittenberg, Germany, but it was not until I undertook a summer internship in Hull that I stumbled upon a fascinating paper about the oestrogen receptor, and perhaps the seed of my interest was sown.

My work at the Max Planck Institute in Dortmund, Germany, was then rewarded with a PhD from the University of Halle-Wittenberg (again). Short research visits to Mill Hill in London and longer ones to Essen, Germany, followed. There I started studying the molecular basis of sulphate activation by PAPS (3'-phosphoadenosine 5'-phosphosulphate) synthases, an incredibly off-beat and blue-sky research topic at that time. Maybe as a consequence, I had tremendous problems in finding a new job appointment, and my mood was not too positive!

THE TURNING POINT

However, in 2012, I was contacted by Professor Wiebke Arlt from the University of Birmingham. This email changed my life. It roughly said, 'We've read your papers and found them really interesting. Please visit us in Birmingham to give a seminar.' Wiebke was interested in my work because in a 2009 landmark paper she had spotted PAPS2 mutations in female patients with androgen excess, linking sulphation pathways and steroidogenesis.

Soon Wiebke and I agreed that I should join the vibrant endocrine department in Birmingham. This sounded so good. I could continue my research, now framed in the biomedical context of steroid hormone regulation with true translational potential. Since starting as a trainee and a foreigner, things have become better and better for me in Birmingham.

MAKING A DIFFERENCE

Climbing an invisible staircase, the award of an Early Career Grant from the Society for Endocrinology for work entitled 'Paving sulphation pathways - novel interaction partners for human PAPS synthases', has allowed me to achieve so much.

First, my research has flourished and I have identified some interaction partners pointing to active proteasomal turnover of PAPS2, now recognised as a central player in steroid sulphation. Even more important, the grant has allowed me to travel to some putative collaboration partners in the UK, Germany and Poland, and given me more credibility for further grant applications.

Aided initially by this support from our Society, I am now fully funded until 2016 by a Marie Curie Intra-European Fellowship, with more publications and applications underway.

AND MUCH MORE BESIDES

Within my first 18 months of membership, the Society for Endocrinology did even more for me. I was able to participate in a superb Career Development Workshop in 2013 (track 2), which included a complete overhaul of my CV, presentation training, a mock fellowship panel interview and lots of networking opportunities.

Then, I was elected a Young Endocrinologists' Steering Group member, which gave me deeper insights into our Society, with many satellite activities during a Society-sponsored visit to this year's Society for Endocrinology BES conference in Liverpool.

Finally, I am about to welcome a Society-funded summer student into my group. This intercalating medical student is surely one of the brightest in her year and will be a valuable additional pair of hands and a welcome critical mind with whom I will be able to discuss the flow of research.

So those are just a few of the reasons why I really love our Society...

JON W MUELLER

Marie Curie Senior Research Fellow, Centre for Endocrinology,
Diabetes and Metabolism, University of Birmingham

The Society's Early Career Grant scheme provides up to £10,000 of funding to help support an endocrine research project. The next application deadline is 27 November 2014. More information can be found at www.endocrinology.org/grants/grant_earlycareer.html.

SOCIETY FOR ENDOCRINOLOGY CORPORATE SUPPORTERS 2014

Platinum Supporter: **Bioscientifica Ltd**

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Pfizer
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For more information, visit www.endocrinology.org/corporate
or contact amanda.helm@endocrinology.org.

CLINICAL UPDATE

3 - 5 NOVEMBER 2014 THE PALACE HOTEL, MANCHESTER, UK

Essential training and clinical practice update for trainees and new consultants in endocrinology and diabetes.

Taught by senior endocrinologists, Clinical Update is based upon the recently revised specialty curricula by the Joint Royal Colleges of Physicians Training Board (JRCPTB).

Covering all eight strands of the curriculum, the interactive three day course provides a comprehensive clinical practice update, alongside indispensable training for those preparing to sit the Specialty Certificate Examination (SCE) in Endocrinology and Diabetes. Workshops include a short seminar followed by a facilitated discussion of case presentations.

KEY DATES

Early bird deadline
1 October 2014

SAVE THE DATE CLINICAL UPDATE 2015

16-18 MARCH 2015

HILTON BIRMINGHAM METROPOLE HOTEL NEC BIRMINGHAM, UK

NEW
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For further information or to request a programme contact

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EVERYTHING'S 'FINE' IN CHICAGO! UK ENDOCRINE NURSES LEAD THE WAY

WRITTEN BY NIKKI KIEFFER



I was lucky enough to be able to attend this year's ICE/ENDO meeting in Chicago. What a busy meeting! If keen enough, you could have been at the meeting from 06.30 in the morning until 20.00 in the evening. I have to confess that I was not there all day every day, but chose my topics wisely. Nevertheless it was quite tiring, but also very rewarding, and I came away with my head spinning with facts.

The most exciting part of the meeting for me was the Nurses' Day. There were excellent presentations and workshops given by nurses from around the globe, including Switzerland, America, New Zealand and Australia. Our American colleagues made us very welcome and were excellent and generous hosts throughout the day.

Six British nurses had been invited to present: Jean Munday and Lisa Shepherd gave an excellent talk on the management of hypoadrenalism, and Phillip Yeoh and Ann Marland ran a helpful workshop on polyuria/polydypsia. The last presentation of the day was given by Chris Gibson and me, and was on the international implications of the Society's Competency Framework for Adult Endocrine Nursing.

At the end of our presentation we were joined on stage by Lisa Shepherd (Chair of the Society for Endocrinology Nurse Committee) and Sofia Llahana (Chair of the European Society of Endocrinology Nurse Committee), and a lively discussion followed. The enthusiasm for the Competency Framework from our European, American and Australasian colleagues is amazing. They have all embraced it and are either already using it or plan to use it in their practice.

'Seventeen of us met for what turned out to be the inaugural meeting of the Federation of International Nurses in Endocrinology'

The discussions continued into the evening reception hosted by our American colleagues and, as a result, a group of us arranged to get together the next day to discuss the next steps. Seventeen of us subsequently met for what turned out to be the inaugural meeting of the Federation of International Nurses in Endocrinology (FINE). Our aim is to collaborate to promote excellence in clinical care by creating an accessible global network of endocrine nurses, thus offering support to our colleagues from countries around the world who may not have the opportunities for advice and support that we currently enjoy.



'The enthusiasm for the Competency Framework from our European, American and Australasian colleagues is amazing'

To this end we have set up a Facebook account as Federation-of-International-Nurses-in-Endocrinology (<http://on.fb.me/1lrVVgC>) and are developing a website. Watch this space!

These are exciting times for endocrine nursing and I am very glad to be involved. I am sure that Lisa will be only too pleased to keep you posted of any further developments in future issues of *The Endocrinologist*.

NIKKI KIEFFER
Endocrine Specialist Nurse, Leicester Royal Infirmary

The second edition of the Society's Competency Framework for Adult Endocrine Nursing is almost complete and will be published in *Endocrine Connections*. More news on this in our next issue.

LISA SHEPHERD NURSE COMMITTEE CHAIR



This summer has seen the continued development of our collaborations with our international nurse colleagues. ENDO 2014 in Chicago provided the perfect background for this. It was good to see so many nurses from the UK and worldwide, not only attending, but also presenting on the Nurses' programme.

Nikki Kieffer, as you will all know as our previous Nurse Committee Chair, has written above about the involvement of the UK nurses and the exciting foundational meeting of the Federation of International Nurses in Endocrinology (FINE). This highlights the importance of developing these global partnerships in order to benchmark, educate and improve patient care. We will keep you informed of any future developments.

I would like to congratulate Jean Munday from Portsmouth for being shortlisted for the Nursing Times Awards. This is a prestigious award and, as described below, recognises nurses who go above and beyond their role. Good luck to Jean for the awards ceremony. Nurses often underestimate the importance of their role and the positive impact they have on patients' lives. Do let us know if you have any achievements you would like to share.

I look forward to reporting on this year's Endocrine Nurse Update, which took place in early September at our new venue in Birmingham, in the next issue of *The Endocrinologist*.

LISA SHEPHERD

ENDOCRINE NURSE TOP HONOURS

The Society sends hearty congratulations to Society member Jean Munday (Portsmouth), who has been shortlisted for Nurse of the Year by the Nursing Times Awards. This award recognises an individual who has gone above and beyond what is expected of them in their day-to-day role and carries out their work on their own initiative with inspiration, determination and creativity to improve patient care or the effectiveness of service provision. Jean is the current Vice-Chair of the Society's Nurse Committee, and we wish her the best of luck at the awards ceremony, which takes place in October.



ESE BASIC ENDOCRINOLOGY COURSE IN REPRODUCTIVE ENDOCRINOLOGY

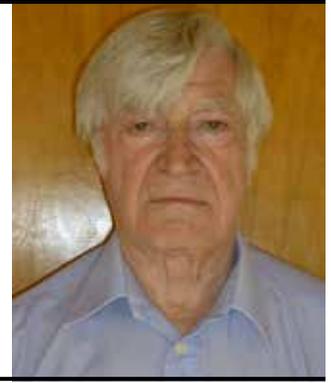
EDINBURGH, UK

18-20 FEBRUARY 2015

- An interactive programme of lectures, workshops and poster presentations featuring leading European and international endocrinologists
- Aimed at early-career basic and translational scientists in endocrinology across Europe to promote learning and collaboration
- Meeting grants are available

For programme and registration details see

www.endocrinology.org/meetings/2015/re2015/



AN INTERVIEW WITH... VINCENT MARKS

INTERVIEW BY MILES LEVY

The doyen of all things hypoglycaemia-related, at 84 years of age, Vincent Marks is one of our most high profile living endocrinologists. He defined the relationship between glucagon and insulin in the early 1960s, and introduced the modern method for measuring blood glucose at low levels. Vincent is the 'go to' man for criminal cases involving insulin murders – he is famously the man who got Claus von Bülow off a 30-year conviction for allegedly killing his wife with insulin (adapted as the Academy Award-winning film *Reversal of Fortune*).

He greets me in the doorway of his Waterloo flat and I am immediately struck by his larger than life presence – short in stature but huge in personality, he is smartly dressed with a thick shock of white hair and an even thicker north-east London accent. 'I was brought up in a pub in Tottenham – nothing too airy fairy', booms Vincent as he recounts his remarkable life story...

EARLY LIFE AND OXFORD

Born of Eastern European Jewish immigrants in 1930, Vincent went to the local grammar school with his brother and sister. He was a rebel in class, always contradicting his teachers. Not being sporty, he was interested in 'anything involving high speed'. He had wanted to be a doctor from the age of five, and got an Oxford scholarship in 1948. He had been rejected the previous year from every medical school in the country; this turned out to be a blessing as he thrived in the liberal world of Oxford. Vincent's clinical apprenticeship at St Thomas' in London was less happy and he 'made few close friends' there, probably because of his anti-establishment tendencies; 'Snobbery was very important in those days.'

CLINICAL CHEMISTRY AND HYPOGLYCAEMIA

Vincent was initially set on a career in psychiatry. He had lined up a job in 1955 with the maverick psychiatrist William Sargant (renowned for physical treatments such as insulin shock therapy and electroconvulsive therapy). Having been refused deferment from the army, Marks was forced to relinquish this possibility, and instead decided to study for his MRCP while working as a senior house officer in clinical pathology at St George's.

There was no set career path and no Royal College of Pathologists in those days (he would later become a founder member and Vice President of this institution). He takes pride in being self-made. 'In order to get on, you needed someone to pull you through, but I never had anybody.' He followed his nose and became a registrar in chemical pathology at London's National Hospital for Neurology, Queen Square. Little did he realise that his interests in clinical medicine, psychiatry and chemical pathology were about to collide beautifully.

Vincent developed a novel method for measuring low blood glucose, making use of a colour change reaction using glucose oxidase.¹ This rendered the tedious Benedict's test obsolete: 'my method became top of the pops'. Marks discovered that many patients with unexplained neurological presentations had profound hypoglycaemia. 'They had a blood sugar of nothing!' he booms. He distinguished acute neuroglycopenia from 'sub-acute neuroglycopenia', the latter presenting with chronic neurological or psychiatric symptoms rather than as an acute emergency. As a relative imposter at Queen Square (being a non-neurologist), Marks had the freedom to study a wealth of pathology from a metabolic angle without treading on anyone's toes. 'No one else was interested so we published everything.'

Marks became an MRC Fellow at King's College London, which he describes as 'a bloody disaster', due to a clash of personalities between supervisors.

Vincent then digresses to relate a fascinating anecdote about RD Lawrence, then Head of Department at King's who, in 1920 as a young physician, developed type 1 diabetes. This was 'a death sentence', as there was no treatment for this condition at the time. Lawrence went abroad to die to avoid upsetting his family, only to be summoned back by his mentor Harrison, who knew of Banting and Best's discovery: 'I've got insulin – it works – come back quick.' Lawrence happily survived and set up a thriving diabetes department; he also co-founded Diabetes UK (then the Diabetic Association) with fellow diabetic HG Wells, to repay his debt to insulin.

Marks' research at King's eventually took an upward turn and, with help from John Anderson and David Pyke, he published on the relationship between Krebs' cycle intermediaries and insulin.^{2,3}

ELLIS SAMOLS AND GLUCAGON

At a Medical Research Society meeting, Marks met someone who was to become a key figure throughout his working life. Ellis Samols, a bright, if eccentric, South African, was extolling the virtues of a new technique to measure insulin called radioimmunoassay (no one else had ever heard of it). Samols had been so excited by the possibilities thrown up by this method that he flew to the USA to learn the technique directly from Sol Berson and Rosalyn Yalow who pioneered it in 1959 (and later won the Nobel Prize).

This greatly influenced Vincent's way of thinking, and he describes Ellis Samols with great affection. 'He was not everybody's cup of tea ... he was not good at personal relationships but we were great friends until he died. He was a bloody genius!'

Marks and Samols forged a prolific collaboration and published seminal papers on the use of insulin measurement to diagnose hypoglycaemia. They showed in the early 1960s that glucagon was a powerful stimulus for insulin secretion, 'the reverse of what everybody thought'.⁴ Together, many years later, they showed that the direction of blood flow in the pancreas was very important. 'The insulin-secreting β -cells carry insulin to the glucagon-secreting α -cells and not the other way round.'⁵

'Marks discovered that many patients with unexplained neurological presentations had profound hypoglycaemia. "They had a blood sugar of nothing!"'

They demonstrated that a glucagon-like substance was released when glucose was ingested by mouth.⁶ 'The idea that glucagon mediated the incretin effect attracted little popular support.' They demonstrated the presence of a glucagon-like reactant in the intestine and, some years later, Marks studied gastric inhibitory peptide (GIP), the earliest pure peptide to be associated with incretin properties, in some detail. It is amazing to think that some 50 years later, these scientific observations underpin the multi-billion dollar industry behind the modern management of type 2 diabetes. Marks proudly recounts how later in life one of the pioneers of gastrointestinal endocrinology, Werner Creutzfeld, exclaimed, 'Ah Vincent – you were right!' after recounting the discovery of glucagon-like peptide-1 as an incretin.

EARLY CONSULTANT LIFE

In 1962, Vincent became Consultant in Clinical Biochemistry and Endocrinology at Epsom District Hospital and West Park Hospital, a large mental hospital. He recalls setting up the chemical pathology lab at Epsom District from scratch.

He continued his interest in spontaneous hypoglycaemia and showed that diazoxide, which was initially introduced as an anti-hypertensive agent, caused hyperglycaemia, particularly in conjunction with thiazide diuretics.⁷ Vincent used this observation to start treating low glucose levels in insulinoma patients (it remains a useful tool some 50 years later).

Marks continued to publish widely, developing an interest in alcohol-related hypoglycaemia, and he collaborated with the Barts group to show that alcohol could cause reversible Cushing's syndrome.⁸ He established himself as the key opinion leader for all matters hypoglycaemia-related. It is an interesting insight into the clinical and intellectual freedom of that exciting era for endocrinology; 'In those days if you heard about an interesting case in a different hospital, you would just go and see them.' He became a founder member of the Royal College of Pathologists and, in 1965, published the first edition of his joint monograph, *Hypoglycaemia*, with Clifford Rose.⁹

SETTING UP THE GUILDFORD LAB

In the 1970s, Marks moved to the University of Surrey as Professor and Guildford Hospitals as Consultant Chemical Pathologist, recognising the possibilities of running a larger laboratory. 'To be successful back then you just had to measure something and apply it.' The Surrey laboratory rapidly became the supra-regional reference centre for the investigation of hypoglycaemia (as it remains today). His unit also pioneered the field of drug level monitoring; previously it was not possible to measure levels of medication such as lithium and phenytoin, something we take for granted today.

Marks became very interested in the recent discovery that insulin was produced as a bigger molecule (proinsulin), then cleaved into insulin and C-peptide. He used this to biochemically distinguish factitious hypoglycaemia (low C-peptide) from endogenous hypoglycaemia (non-suppressed C-peptide). 'They said C-peptide didn't do anything, but it became essential to the diagnosis of insulinomas.' He remains a big proponent of C-peptide's likely importance in normal physiology. 'One day C-peptide will be added back to exogenous insulin in the treatment of diabetes.'



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GIN AND TONIC

Vincent then proceeds to mention his 1977 *Lancet* publication 'Lunchtime gin and tonic a cause of reactive hypoglycaemia'.¹⁰ (Honestly, he related this whilst pouring me a healthy measure of gin and tonic!) This paper was controversial and 'caused quite a commotion'.

Unimpressed by the fashionable diagnosis of 'reactive hypoglycaemia', Marks decided to study it. He showed that a combination of glucose and alcohol was required to achieve a significant insulin response, and not just one of glucose alone. He suggested that alcohol-mediated hypoglycaemia was an important cause of car accidents in the late afternoon. Marks dismissed reactive hypoglycaemia as a glib diagnosis made by physicians who knew little about glucose metabolism. Throughout the interview, Marks clearly has distaste for fashionable non-evidence-based medicine and 'quacks'.

MELATONIN AND JET LAG

In the 1980s, a bright Swiss post-doc scientist named Josephine Arendt joined Vincent at Guildford. Arendt had developed an assay for the hormone melatonin. Marks and Arendt published seminal papers on melatonin and jet lag, including the first clinical trial using native melatonin.¹¹ Arendt became 'the Queen of Melatonin'.

Marks later took a back seat on melatonin. As he comments, 'I knew bugger all about biological rhythms – I pulled out as soon as Josephine was able to take over.' During this same period, Vincent developed assays for insulin-like growth factor-I (IGF-I) and IGF-II, helpful in the diagnosis of non-islet cell tumour hypoglycaemia.¹² He was joined by the highly regarded scientist Peter Flatt, who renewed Marks' interest in gut peptides, and together they published important work on GIP as an obesity hormone.¹³

'In those days, if you heard about an interesting case... you would just go and see them.'

‘Having looked at the evidence, Vincent was convinced of von Bülow’s innocence, and was instrumental in having the conviction overturned’

THE MEDICO-LEGAL YEARS

Marks observed throughout his career that ‘hypoglycaemia virtually never kills you except in type 1 diabetes’. After all, insulin shock therapy saw hundreds of units of insulin injected intentionally to treat people with severe psychiatric illness with remarkably few problems.

In the 1980s, a high society couple were making front-page headlines across the Atlantic. Unbeknown to Vincent, his career was to take a global trajectory into medico-legal matters. Sunny von Bülow, an American heiress, had been found comatose at home with low blood glucose. Her husband, Claus, was accused of injecting her with insulin and was initially found guilty of attempted murder and sentenced to 30 years’ imprisonment. Because of his academic track record in hypoglycaemia, Marks was invited to be an expert witness at von Bülow’s appeal hearing. Having looked at the evidence, Vincent was convinced of von Bülow’s innocence, and was instrumental in having the conviction overturned.

This was the first ever televised criminal trial in the USA and achieved such notoriety that a screenplay was written for the film *Reversal of Fortune*, which won an Academy Award, with Jeremy Irons and Glenn Close playing Claus and Sunny respectively.

Marks subsequently became the key international figure in medico-legal issues relating to hypoglycaemia from suspected foul play. His book *Insulin Murders: True Life Cases*¹⁴ chronicles true-life cases with which he has been involved, including the infamous nurse Beverly Allitt who murdered children by injecting them with insulin. Vincent gives a fascinating insight into the medico-legal world. Many so-called expert witnesses used in law it seems are not truly the best opinions; as he remarks, ‘You can’t do it on the cheap or else you get people who know bugger all!’

Marks feels so strongly that high profile cases need the right experts to achieve justice that he now often gives his opinion ‘pro bono’ when asked to advise on such matters.

‘He remains a big proponent of C-peptide’s likely importance in normal physiology. “One day C-peptide will be added back to exogenous insulin in the treatment of diabetes.”’

POLITICS AND THE NHS

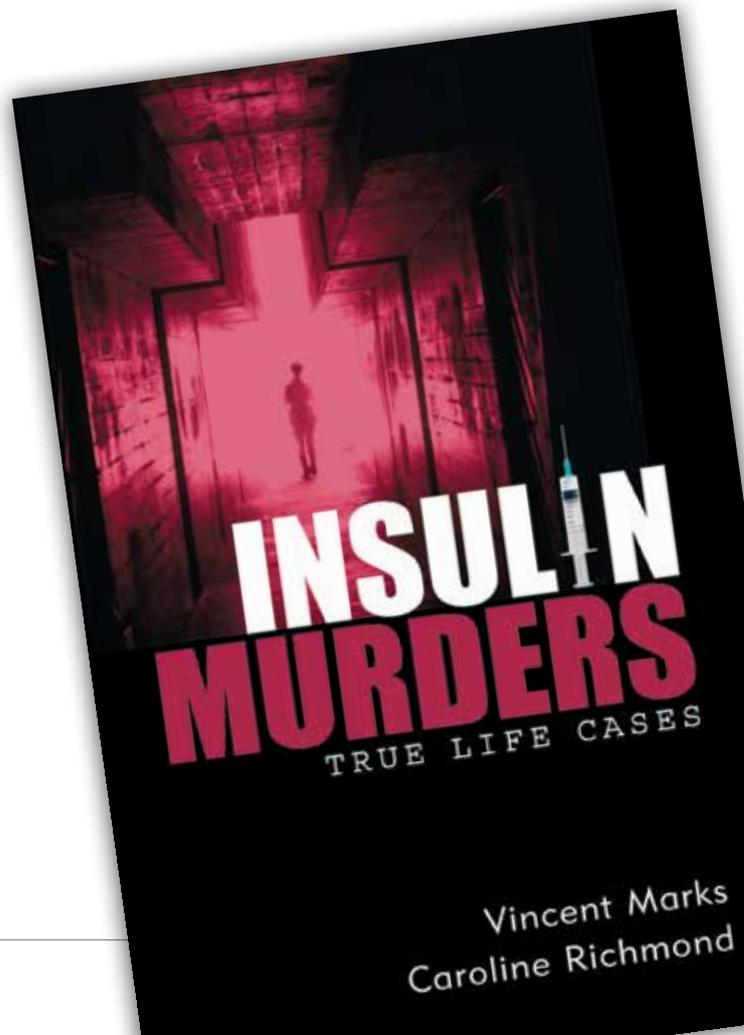
Vincent always thought his GP brother John was the political member of the family. John Marks became Chairman of the British Medical Association in the 1980s and famously led the charge against Kenneth Clarke and Margaret Thatcher’s internal market and purchaser-provider split (I remember this in the news when I was at school). Vincent has gradually drifted into the political side of medicine himself, despite thinking this was his brother’s job.

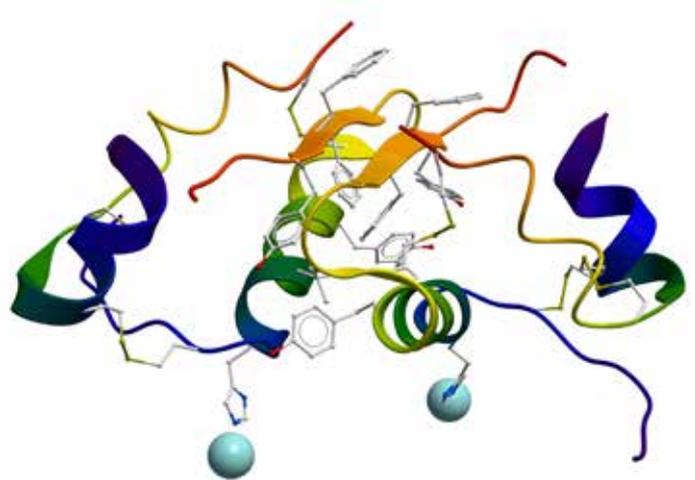
Continuing his dislike of medical fraudsters, in 1991 he jointly set up a charity named HealthWatch (www.healthwatch-uk.org; not to be confused with the government-funded Healthwatch England). The President is broadcaster Nick Ross of TV *Crimewatch* fame.

Vincent believes the medical establishment has been emasculated over the years by politicians. ‘When Bevan introduced the NHS, every level of management had a statutory Medical Advisory Committee. Thatcher was never exposed for abolishing these ... and Blair carried it on.’ He has become frustrated with the over-managed NHS but acknowledges that previously there was probably too little supervision of clinicians. He believes the Beverly Allitt case would never have been as bad if the department in question had not been so dysfunctional.

REFLECTIONS OF PAST, PRESENT AND FUTURE

Marks’ career flew and in his prime he became Dean of the Faculty of Science, Vice President of the Royal College of Pathologists and President of the Association of Clinical Biochemists (not bad for the Jewish boy brought up in a pub).





Human insulin molecular structure ©123RF STOCK PHOTOS

Despite these achievements, at heart Vincent is a die-hard clinical chemical pathologist. He takes great pride that his 1959 paper on measuring low glucose was re-issued as a landmark paper in the 40th anniversary of *Clinica Chimica Acta* (the international journal of clinical chemistry and diagnostic laboratory medicine).¹⁵ Having never been one for sentiment (he is a tough old bird), he has found himself re-engaging with his Oxford College (Brasenose) and recognises the profound importance of those halcyon days, and the importance of his collaborations within endocrinology.

His colleague Arnold Bloom sent his bright son Steve to him for advice. 'I told him gut hormones were interesting but probably not good enough for a career – fortunately he ignored my advice!' On another occasion a young doctor named George Alberti came to him for career guidance and Vincent suggested that he ought to try out chemical pathology (this time Vincent's advice seems to have been better judged).

Vincent Marks is a bon viveur and family man. 'I belong to the school that believes life is not a rehearsal but the real thing. I've always felt it is important to have a good life as well as my career.'

He shares his time between his Waterloo town pad (which has a fantastic view of St Paul's Cathedral) and Haslemere in Surrey. At the age of 84 he still feels (and looks) young. As he says, 'When I'm old we will probably spend most of the time here in London as it's easier to get around.' His apartment is filled with sculptures that his wife has made. ('She was a brilliant sculptor but unfortunately for her she married me.')

'Ellis Samols was not good at personal relationships... but he was a bloody genius!'

Marks is 5 years his wife's senior. They met in 1956 at his good friend Stanley Feldman's wedding. 'In those days because I was 5 years older than her I had to be her guardian until she was 21!' Feldman and Marks remain close, having written a book in 2009 magnificently entitled *Global Warming and Other Bollocks*¹⁶ as well as another, *Panic Nation*¹⁷. Vincent has a daughter and a son (a judge and a QC) and his grandchildren are now growing up and starting careers of their own (one is a talented musician and has moved to Boston).

I have been with Vincent for several hours and it is time to get the train back home (I am starting to feel the gin and tonic hypoglycaemia). As I get the cab back to King's Cross, I reflect on our meeting. I have unwittingly had the best tutorial ever on the investigation of hypoglycaemia. Intrinsicly I was comfortable in Marks' company, I think partly because his background is so similar to my own heritage (his accent takes me back to my dad's golf club when I was growing up – full of vibrant East End Jewish people who had escaped tragedy and poverty though one means or another).

Marks has the air of a bare-knuckle fighter who has come out on top. His warmth and directness are both familiar and refreshing. He has clearly had a massive influence on our specialty and once again I am left wondering who is going to replace the great characters of endocrinology. In Vincent Marks' case, I don't think we should try, as this man is almost certainly a one-off.

MILES LEVY
Editor, The Endocrinologist

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NEW THYROID CANCER GUIDELINES

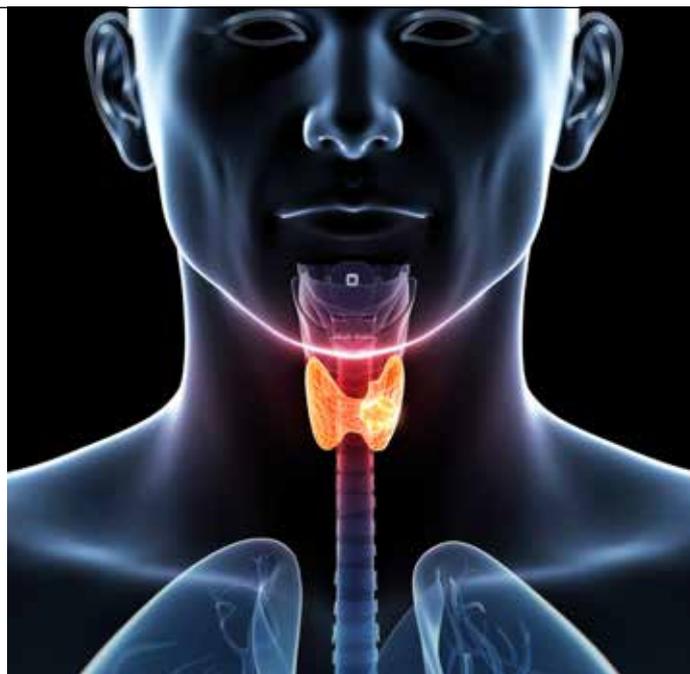
The British Thyroid Association has recently published updated guidelines on the management of thyroid cancer. They can be found in *Clinical Endocrinology* 2014 **81** (supp 1) 1–122.

The paper is open access and is available via <http://bit.ly/1ralxFD>.

NEW GUIDELINES ON RARE ADRENAL TUMOURS

The Endocrine Society has issued new clinical practice guidelines on the diagnosis and treatment of pheochromocytomas and paragangliomas, published in *Journal of Clinical Endocrinology & Metabolism* 2014 **99** 1915–1942.

A free copy of the guidelines can be downloaded at <http://dx.doi.org/10.1210/jc.2014-1498>



VANISHPOINT SAFETY SYRINGES



The Addison's Disease Self Help Group is pleased to announce that Vanishpoint safety syringes are now available to purchase in their web shop. Vanishpoint integrated, retractable syringes are available in sets of 2 or 5, with disposable Amp Snaps to take

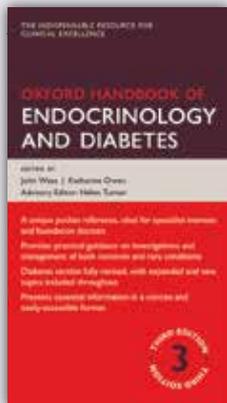
the top off glass vials and photo instructions for use with Efcortisol or Solu-Cortef. Please note, these prescription drugs are not supplied with the injection materials in this kit.

Visit www.addisons.org.uk/shop for further details.

REVIEW

OXFORD HANDBOOK OF CLINICAL ENDOCRINOLOGY AND DIABETES

J Wass & K Owen (Eds), Oxford University Press, 2014, 3rd edn, 928pp, pbk, £34.99, ISBN 978-0-19-964443-8



It's back – the latest version of this essential guide to clinical endocrinology and diabetes, the friend of the registrar and the aide-mémoire of the more experienced clinician. I was previously very au fait with the first edition, both in hard copy and iPhone App format, and really enjoyed its thoroughness and concise nature. However, the former was stolen (as it had been left in a clinic room – highly desirable as it is), and the latter was no longer accessible as I 'betrayed' Apple and took on an Android phone. This meant that I could no longer use the very usable App (despite the £35 I had paid for it – yes £35 for an App!).

content, this has been revised in line with recent developments in the field, such as the latest on primary hyperparathyroidism, a good transgender endocrinology section, reproductive endocrinology and more up to date information on obesity.

This remains a text heavy volume and, for the sake of readability, could arguably benefit from more in the way of illustrations and diagrams and less compressed text. The dictat of the subject per page format can sometimes leave things wanting. One other failing of this otherwise excellent book is the difference in approach and style from the *Oxford Handbook of Clinical Medicine*. If you take a look at the endocrinology section of that text, you tend to get far more of a feel for the philosophy and history of the speciality, along with some good pictures and anecdotes. Although not essential, it does help to draw the reader into the intricacies and excitement of our chosen speciality.

So what has changed for the third edition? First, there is an expanded and updated section on diabetes to include new helpful content, such as using a continuous glucose monitoring system and interpreting downloads, by Pratik Choudhary and colleagues. Overall though, I don't think that diabetes has as much coverage as it should and that it potentially justifies a whole *Oxford Handbook* all of its own. With regard to the endocrine

However, this should not stop the committed endocrinologist from getting hold of a copy of this new volume as soon as possible, to ensure that we stay informed and conscientious in our clinical care.

PAUL GRANT
Consultant Endocrinologist,
Royal Sussex County Hospital, Brighton

2014 UNDERGRADUATE ESSAY COMPETITION

The Society received 69 entries to this year's Undergraduate Essay Competition. Each was marked and ranked by a distinguished panel, who were once again impressed by the high standard of submissions. The top prize of £1,000 went to Emma Smith (Warwick). An abbreviated version of her essay appears here; you can read the full, referenced version at www.endocrinology.org/grants.

TO BAT OR TOO FAT? THAT IS THE QUESTION...

How can we facilitate sustainable weight loss in patients with obesity, including those with type 2 diabetes? Dietary changes are difficult to sustain, and there is a hiatus in the market for safe and effective weight loss therapies. Bariatric surgery is inaccessible to many due to its prohibitive cost. So what next? Current, exciting research is turning to brown adipose tissue (BAT).

BAT is important in small rodents and neonates. It is unique in having a capacity to induce facultative non-shivering thermogenesis (NST) under sympathetic nervous system (SNS) control, by uncoupling oxidative phosphorylation and facilitating dissipation of energy as heat.

Whilst the existence of BAT in human neonates has been known for many decades, interest in this field was rekindled in 2009, when metabolically active areas of BAT in *adult* humans were demonstrated for the first time. This BAT was shown to increase in metabolic activity in response to cold exposure, offering the prospect of enhancing energy expenditure through stimulation of BAT activity in obese individuals to facilitate weight loss: a potential novel therapy.

Although exposure to the cold may, with time, result in weight loss through activation of BAT, this is unlikely to be popular and may have associated health risks. Thankfully, there are other means of stimulating BAT independent of temperature change. The process of BAT thermogenesis consists of two main pathways: (i) the physiological, 'classical' route, through which BAT undergoes hypertrophy and hyperplasia in response to, for example, cold and SNS stimulation, and (ii) a process known as 'browning' of white adipose tissue (WAT). Studies in rodents have shown the appearance of brown adipocytes within areas of WAT in response to cold stimulation, forming 'brite' or 'beige' adipocytes.

Therapeutic exploitation of the pathways that convert WAT into beige adipocytes would facilitate enhanced energy expenditure concurrent with diminishing WAT stores in obesity, a truly awesome combination of effects for obese patients.

But how to stimulate this 'browning' effect? A clinically viable solution would require a novel drug. To develop a drug, a target is required. BAT is physiologically activated by the SNS, but this presents a problem for drug development. Given the plethora of systems that respond to 'fight or flight' (resulting from SNS activation), substantial challenges lie in targeting the SNS to enhance solely BAT thermogenesis by the 'classical' route.

Rather than targeting the SNS or even BAT directly, one could develop therapies that influence BAT indirectly: novel precursors and activators that originate outside the central nervous system (CNS) and have recently been shown to induce 'browning' of WAT, as follows.

a) Thyroid: BAT contains a thyroid hormone-specific enzyme, thyroxine 5'-deiodinase, which binds norepinephrine (from the SNS), enabling conversion of thyroxine to active tri-iodothyronine. This subsequently induces uncoupling protein-1 (UCP-1) gene transcription: the mitochondrial enzyme in BAT which produces heat through NST.

b) Liver: Bile acids actually activate 5'-deiodinase in BAT, by interacting with G protein-coupled bile acid receptor TGR. Furthermore, it has been demonstrated that through binding to the same receptor, bile acids can lead to release of glucagon-like peptide-1 (GLP-1) in the intestines, which in turn induces BAT thermogenesis. A further role for the liver implicates fibroblast growth factor 21. In rodents, this binds to the FGF receptor cell complex in BAT, stimulating mitochondrial uncoupled respiration, glucose oxidation and 'browning' of WAT, promoting weight loss and anti-diabetic effects.

c) Skeletal muscle: Irisin, a protein released from muscle in response to exercise, has been shown in rodent models to induce WAT 'browning' and protect against obesity. The connection with exercise is particularly interesting, as it could highlight a therapeutic opportunity (an 'exercise pill') for administration of exogenous irisin in obese subjects who find it difficult to exercise.

d) Immune system: In response to cold, macrophages in rodent models were activated in BAT to produce norepinephrine, a process which was shown to be central to BAT-induced thermogenesis in response to cold exposure. Further research may reveal more data on immune-mediated BAT thermogenesis.

These known mediators of BAT activity offer new areas of research and drug development that avoid CNS targeting and its inherent dangers. The complexity of endocrine feedback loops make targeting BAT via any route challenging. Although recent BAT research offers new hope, we have incomplete understanding of how the various mediators of BAT activity interact. Enhancing energy expenditure through BAT activation is likely, over time, to induce a counteracting homeostatic mechanism to redress any weight loss. This further challenge will need to be overcome through novel approaches.

EMMA SMITH

Undergraduate student, University of Warwick

Congratulations also to the runners up who each received £250:

Aws Sadik (Cambridge), Irfan Jumabhoy (London), Rajan Patel (Oxford) and Mihir Sanghvi (London).

Are you an undergraduate with a passion for endocrinology? Why not enter our 2015 Undergraduate Essay Prize competition? You could win £1,000! The deadline is 11 February 2015. Find out more at www.endocrinology.org/grants

LESSONS TO LEARN? EVALUATING TEACHING IN HIGHER EDUCATION

WRITTEN BY ROSEMARY BLAND



Back in March, I hopped on a train to London to attend a workshop on 'Improving the status and evaluation of teaching in higher education', part of a joint project undertaken by the Academy of Medical Sciences, The Physiological Society, the Heads of University Biosciences and the Society of Biology.

Why did I go? Well, I have taught students for almost 20 years and have a particular interest in medical education, so when the Society for Endocrinology asked if I'd be interested in attending, I jumped at the chance.

One aim was to discuss processes for evidencing and evaluating good teaching. When I did my degree, if you had a bad lecturer you simply spent longer in the library looking up the material that hadn't been taught! Aren't we lucky that attitudes have changed and teaching is now considered important? However, assessing quality presents challenges.

WHY SHOULD WE ASSESS TEACHING QUALITY?

It's simple, 'The quality of tomorrow's research, and the knowledge and skills of our future graduates, all depend on the quality of today's teaching.'¹ There are also some very practical aspects. Recruiting students is vital, as student fees are an important source of income and teaching reputation is one aspect that prospective students consider. The introduction of higher fees means that students are now considered customers, and they expect value for money. There has also been a cultural shift, and teaching is considered important, with evidence of teaching quality and impact often used in annual appraisals and as part of the promotion process.

HOW DO WE ASSESS TEACHING QUALITY?

If you are a researcher, the quality of your research can be judged by your papers or your grant income. While these might be flawed, they are quantifiable. Are there similar measures we can use to assess teaching quality and effectiveness? If you ask that question, people will probably tell you that you could use student or peer evaluation, but are they reliable and robust?

If student evaluation is voluntary, you are likely to find it is completed by students with strongly held opinions (positive or negative). The time at which evaluations are gathered relative to the teaching sessions matters. A period of reflection might help, but are recollections then accurate? Popularity with students isn't necessarily a result of good teaching. What about peer assessment? It's very difficult to be critical of your colleagues. If that assessment feeds into a review or promotion process, is it reasonable to expect your peers to do it?

What do we hope to achieve when we teach? I mostly teach medical students and I hope to engage them in the subject, promote lifelong learning and develop their skills and knowledge to be safe doctors (this is equally applicable to other sciences). Could you use evidence that student learning has been effective as a surrogate marker of teaching skills? What about using exam results? Two problems are immediately apparent. Exams are primarily designed to assess the students not the staff, and, however professional we are, if we know we are being judged by student success, why would we set difficult questions?

There are other indicators of quality: self-reflection, support and mentorship, external roles and recognition and scholarship, which might include grant income and publications. By now you will have realised that there isn't a simple way to do this. A combination of different assessment measures, taken together to give a picture of the teacher as a whole, is the most robust measure of quality.

However, most institutions have their own descriptors of quality and tools to assess it. Can we ensure consistency between institutions? One option is membership of a professional body. The Higher Education Academy (HEA) runs a well-recognised fellowship scheme and the Association of Medical Educators runs a very similar scheme for medical teachers. Both have a framework of professional standards that are increasingly used to measure teaching competence and excellence.

'The quality of tomorrow's research, and the knowledge and skills of our future graduates, all depend on the quality of today's teaching.'

HOW CAN WE IMPROVE TEACHING QUALITY?

Key to this is the open sharing of good practice and mentorship of junior staff. In an attempt to promote teaching excellence, some institutions are encouraging all their staff to become fellows of the HEA (or equivalent). The number of 'teaching-only' staff is increasing. Is this good and does it matter what they are called? Are titles such as 'teaching fellow' instead of 'lecturer' seen by students as positive or negative, and are teaching-only staff perceived differently by their colleagues?

On the journey home I reflected on the day. Although teaching contributions may still be undervalued and evaluation of quality is challenging, there are dedicated people who are working hard to improve both the status and evaluation of teaching, and attitudes towards teaching are changing.

ROSEMARY BLAND

Associate Professor, Warwick Medical School, University of Warwick

Rosemary is a member of the Society for Endocrinology's Science Committee. Her research focuses on the molecular endocrinology of vitamin D in a variety of tissues and diseases. She teaches undergraduate biology and on the MB ChB programme at Warwick Medical School. She also lectures on endocrinology and bone disorders and teaches postgraduate CPD modules.

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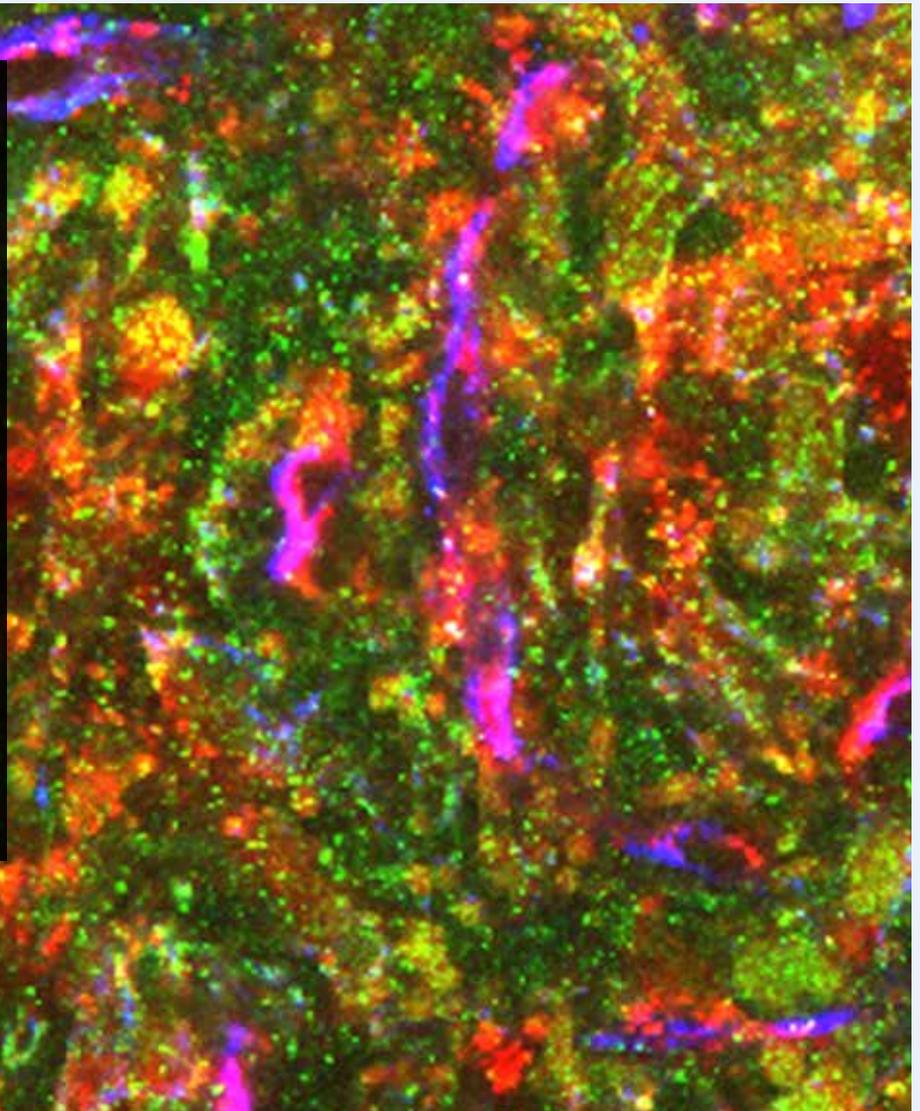
IMAGES IN ENDOCRINOLOGY

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

COVER IMAGE FROM *JOURNAL OF ENDOCRINOLOGY* JULY 2014

The image depicts localisation of platelet-derived growth factor beta (PDGF β) in the neurohypophysis of an adult mouse. The immunoreactivity of PDGF β (green) is observed at oxytocin-containing axonal terminals (red) but not endothelial cells (blue).

Credit: **E Furube, T Mannari, S Morita, K Nishikawa, A Yoshida, M Itoh and S Miyata**, Department of Applied Biology, Kyoto Institute of Technology, Japan



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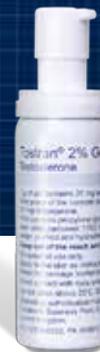
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2% TESTOSTERONE GEL.
HALF THE GEL REQUIRED
VERSUS 1% GEL AT
EQUIVALENT DOSE^{1,2}

CONVENIENT 60G CANISTER
FOR REDUCED MESS/WASTAGE.¹
ELIMINATES THE NEED FOR
MULTIPLE TUBES OR SACHETS



THE FIRST METERED DOSE 2% TESTOSTERONE GEL

Tostran[®] (testosterone) 2% Gel Prescribing Information

Please refer to the Summary of Product Characteristics (SPC) before prescribing.

Presentation: Tostran 2% Gel, contains testosterone, 20 mg/g. **Indication:** Replacement therapy with testosterone for male hypogonadism when testosterone deficiency has been confirmed by clinical symptoms and laboratory analyses. **Dose:** The starting dose is 3 g gel (60 mg testosterone) applied once daily to clean, dry, intact skin, on the abdomen or to both inner thighs. Adjust dose according to clinical and laboratory responses. Do not exceed 4 g of gel (80 mg testosterone) daily. Apply after washing, bathing or showering. Do not apply to the genitals. Do not use in women, or children under the age of 18 years. **Contraindications:** Known or suspected carcinoma of the breast or the prostate. Hypersensitivity to any of the ingredients. **Special warnings and precautions for use:** Not to be used to treat non-

specific symptoms suggestive of hypogonadism if testosterone deficiency has not been demonstrated and if other aetiologies have not been excluded. Not indicated for treatment of male sterility or impotence. Pre-examine all patients to exclude a risk of pre-existing prostatic cancer. Perform regular monitoring of breast and prostate. Androgens may accelerate the development of subclinical prostatic cancer and benign prostatic hyperplasia. Oedema with/without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal or hepatic disease. Discontinue immediately if such complications occur. Use with caution in hypertension, ischemic heart disease, epilepsy, migraine and sleep apnoea as these conditions may be aggravated. Care should be taken with skeletal metastases due to risk of hypercalcaemia/hypercalcauria. Androgen treatment may result in improved insulin sensitivity. Inform the patient about the risk of testosterone transfer and give safety

instructions. Health professionals/carers should use disposable gloves resistant to alcohols.

Interactions: Androgens can increase the anticoagulant effect of anticoagulants. Concurrent administration with ACTH or corticosteroids may increase the likelihood of oedema. **Side-effects:** *Very common:* application site reactions (including paresthesia, xerosis, pruritis, rash or erythema). *Common:* increased haemoglobin and haematocrit, increased male pattern hair distribution, hypertension, gynaecomastia, peripheral oedema, increased PSA. **May cause irritation and dry skin.** Consult SPC for further details of side-effects. **Pack Size and Price:** Packs containing one or three 60 g metered-dose canisters per pack. Price £28.67 per canister. **Legal Category:** POM. **Marketing Authorisation Holder:** ProStrakan Limited, Galabank Business Park, Galashiels, TD1 1QH, UK. Marketing Authorisation Number: PL16508/0025 ©ProStrakan. ®Registered Trade Mark. Date of PI Preparation: November 2013.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to ProStrakan Ltd on 01896 664000.

References: 1. Tostran[®] Summary of Product Characteristics, June 2010. 2. Testogel[®] Summary of Product Characteristics, November 2006.
Date of preparation: February 2014. **Job code:** M015/1224