

THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

The Science behind Sex

Tales of Sopranos and
Transsexuals, Eunuchs
and HRT, Disruptors
and Offenders

**+ SECRETS FROM
THE SEX THERAPIST...**

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A WORD FROM THE EDITOR...



Welcome to this erotically themed summer issue, which confirms that we endocrinologists are definitely the best when it comes to sex! Inside the pages of this magazine filled with explicit facts, we read about the science behind sex, gender and puberty, and the dilemmas of hormone replacement in men and women (pages 6–15). We learn about sex hormone receptors, endocrine disruptors, and our sex therapist recounts her 'Tales of the Unerected' (cue the theme tune from that 1980s Anglia TV series).

Talking of erotic dancing, on pages 20–21 you will read an exclusive interview with the Society's incoming President Steve O'Rahilly, who has recently been seen cutting some serious shapes of his own on the dance floor (and other surfaces) at the Society for Endocrinology BES conference dinner.

So summer is here and we are getting in touch with all things Brazilian. As we complete our Panini World Cup Sticker Albums (I have some swaps if anyone is interested), pack our bags for ICE/ENDO 2014, and enjoy a pheromone-filled summer, we continue to have another superb year in endocrinology.

Please take the time to read the fantastic feature articles inside this issue, which are both entertaining and genuinely educational. Thanks as always to those who continue to contribute to this magazine, making it a welcome little supplementary boost to our endocrine lives!

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Associate Editor:

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Dr Olympia Koulouri (Cambridge)

Managing Editor: **Dr Jennie Evans**

Sub-editor: **Caroline Brewser**

Design: **Third Floor Design**

Society for Endocrinology

22 Apex Court, Woodlands,

Bradley Stoke, Bristol BS32 4JT, UK

Tel: **01454 642200**

Email: info@endocrinology.org

Web: www.endocrinology.org

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THE ENDOCRINOLOGIST ENQUIRIES

Please contact **Jennie Evans**

endocrinologist@endocrinology.org

ADVERTISING

Please contact

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

The Society welcomes news items, contributions, article suggestions and letters to the Editor.

We would also like to hear your feedback on this issue of the magazine.

Deadline for news items for the Autumn 2014 issue: 1 July 2014. Deadline for news items for the Winter 2014/15 issue: 19 September 2014.

INCREASED SUBMISSIONS TO SOCIETY JOURNALS

Between 2012 and 2013, Society for Endocrinology journals saw magnificent increases in submissions.

Endocrine-Related Cancer up 40%

Journal of Molecular Endocrinology up 20%

Journal of Endocrinology up 6%

And the Society's official clinical journal, *Clinical Endocrinology*, also continues to thrive and attract high submissions.

We are delighted to see such an impressive increase in interest, and thank the Editorial Board members who handle the papers and ensure that the journals continue to make a contribution to the scientific and medical community.

ENDOCRINOLOGISTS ON TV



2014's explosion of science programmes on the BBC has ranged from Brian Cox's drama on the invention of radar to Eddie Izzard's coverage of a clinical trial in Parkinson's disease. On the crest of this scientific wave rode top UK endocrinologist and past Society for Endocrinology Chairman Professor John Wass (Oxford).

John appeared on BBC Four to tell the story he's wanted to tell all his life – the history of hormones. In *The Fantastical World of Hormones*, which aired in late February, he touched upon the best and worst of medical history, accompanied by Professors Saffron Whitehead (London) and Sadaf Farooqi (Cambridge). Viewers learnt that, as recently as the 19th century, boys were castrated to keep their pure soprano voices, as well as how juices were extracted from testicles in the hope they would rejuvenate old men and how true medical heroes like Frederick Banting discovered a way to make insulin, thus saving the lives of countless diabetes sufferers.

The same week saw Professor John Bevan (Aberdeen) appear on BBC's *The One Show* to tell how he diagnosed a patient with acromegaly through seeing her on tv. Sister Aelred appeared on one of the first episodes of *The One Show* where Professor Bevan noticed she was speaking as though her tongue was too big for her mouth. John contacted the show with his concerns and the diagnosis proved correct. Sister Aelred has since undergone surgery and is recovering well.

NEW GUIDELINES ON HYPONATRAEMIA

New clinical practice guidelines have been published on the diagnosis and treatment of hyponatraemia, and were produced by the European Society of Endocrinology, the European Society of Intensive Care Medicine and the European Renal Association–European Dialysis and Transplant Association. For a free copy, see *European Journal of Endocrinology* 2014 170 G1–G47 (www.eje-online.org/content/170/3/G1.full).

OFFICERS' VACANCIES

Professors David Ray, Graham Williams and Chris McCabe will complete their terms of office as General Secretary, Treasurer and Programme Secretary respectively at the 2015 AGM. Replacement officers are therefore sought, to begin their periods as officers-elect in November 2014 before taking up full office at the 2015 AGM for a period of 3 years (General Secretary and Programme Secretary) or 5 years (Treasurer). Job descriptions and the responsibilities of Trustees and Directors can be found at www.endocrinology.org/about/committee/council.html.

Council has nominated Professor Karen Chapman for the position of General Secretary, Dr Barbara McGowan for Treasurer and Professor Simon Pearce for Programme Secretary. If any member wishes to make further nominations by 3 July 2014, please contact members@endocrinology.org for a nomination form.

CLINICAL CASES MEETINGS SUCCESS



CLINICAL CASES

The Society has been celebrating excellent feedback from the recent Clinical Cases meetings, which provided clinical endocrinologists with forums to discuss notable cases. The Regional Clinical Cases meeting in Belfast in December with the Irish Endocrine Society was attended by more than 60 delegates, 20% of whom were not Society members. The first prize for an oral communication went to Una Graham (Belfast) for her work on familial hypocalcaemic hypercalcaemia.

The National Clinical Cases meeting in London in February, in association with the Royal Society of Medicine, attracted 90 clinicians, who listened to cases ranging from acromegaly to hyperinsulinism. Ben Challis (Cambridge) took first prize for his work on hyperinsulinism.

CONGRATULATIONS...

Society member John Honour was named in a recent list by the Science Council as one of the 100 leading UK practising scientists. John is recognised 'for his expertise in developing, testing and exploiting devices for use in the operating theatre, so taking the laboratory to the bedside'.



SOCIETY CALENDAR

15-16 September 2014

ENDOCRINE NURSE UPDATE
Birmingham

17-19 October 2014

CAREER DEVELOPMENT WORKSHOPS
Steventon, Oxfordshire

3-5 November 2014

CLINICAL UPDATE
Manchester

see

www.endocrinology.org/meetings for full details



GRANT AND PRIZE DEADLINES

16 June-14 July 2014

UNDERGRADUATE ACHIEVEMENT AWARDS

15 August 2014

CONFERENCE GRANTS

27 November 2014

EARLY CAREER GRANTS

see

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

SOCIETY AT ICE/ENDO 2014

The Society will have an exhibition stand at the joint meeting of the International Society of Endocrinology and the Endocrine Society (commonly known as ICE/ENDO 2014) which is taking place in Chicago, USA, on 21–24 June. If you are planning to attend, come and see us at stand 1315.

WITH REGRET

We are sorry to announce the death of Senior Member Professor Werner Schlegel of Münster, Germany.

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

Perinatal BPA exposure disrupts stress responses

Endocrine-disrupting chemicals (EDCs), such as bisphenol A (BPA), are found in many household and industrial products. These chemicals interfere with hormone synthesis, secretion, action or elimination, resulting in various health problems. In 2013, controversy over the regulation of EDCs erupted, with debate between toxicologists and endocrinologists focusing on whether low-dose effects of EDCs should prevent a safe threshold for compounds being set.

Panagiotidou and colleagues have studied the effect of a low chronic exposure of BPA during the perinatal period on the stress-induced hypothalamic-pituitary-adrenal (HPA) axis response of rats at puberty. The dose used in the study was below the equivalent lowest observed adverse effect level (LOAEL) for humans. They found that the HPA axis was altered following BPA exposure in both basal conditions and following stress, and was sexually dimorphic. These results provide further evidence that regulation of EDCs should take into account the low-dose effects of these chemicals.

Read the full article in *Journal of Endocrinology* 220 207–218

JOURNAL OF MOLECULAR ENDOCRINOLOGY

AGEs contribute to osteopenia in diabetes

Osteoporosis is a common complication of diabetes mellitus and is associated with a reduction in bone formation. Advanced glycation end products (AGEs), formed through non-enzymatic reactions between carbohydrates and proteins or lipids, and oxidative stress (OxS) have roles in the development of various diabetic pathologies and may also contribute to the development of osteopenia.

In this study, Weinberg and colleagues investigated the mechanisms by which AGEs and OxS cause osteopenia. They found that AGEs induce the apoptosis of bone marrow stromal cells (BMSCs) through a pathway involving the production

of TNF α , p38 MAPK signalling and OxS. The effects seen in BMSCs probably also extend to the osteoprogenitor cell population, suggesting a reduction in the number of cells available for bone remodelling and regeneration.

AGEs have also been reported to suppress the osteoblastic differentiation of bone marrow stromal stem cells. Thus, hyperglycaemia and the production of AGEs provide a multifaceted mechanism for the development of osteopenia through the loss of osteoprogenitor cells.

Read the full article in *Journal of Molecular Endocrinology* 52 67–76

ENDOCRINE-RELATED CANCER

Histone modifying enzymes as prostate carcinoma markers

Biomarkers are used to screen and characterise prostate carcinomas. Deregulation of histone modifying enzymes – histone methyltransferases (HMTs) and histone demethylases (HDMs) – has been associated with prostate carcinoma development and progression. These may represent biomarkers that can more effectively predict disease stage and aggressiveness leading to improved therapeutic management.

Vieira and colleagues screened 37 HMTs and 20 HDMs in prostate cancer samples. Changes in gene expression levels were found for several genes, of which 5 HMTs and 4 HDMs were investigated further in 150 prostate carcinoma samples. The HMT PRMT6 discriminated between prostate carcinoma tissue

and normal tissue with the highest sensitivity and specificity. Interestingly, increased expression levels of the HMT SMYD3 were associated with advanced disease, and may be useful as a predictor of disease progression.

The profiling of histone modifying enzymes, particularly SMYD3, may be useful in the clinical assessment of prostate cancers and aid therapeutic management of the disease. Further research is required to assess the mechanistic involvement of these histone modifying enzymes in disease progression and their potential use as therapeutic targets.

Read the full article in *Endocrine-Related Cancer* 21 51–61

ENDOCRINE HIGHLIGHTS

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

Diagnosing pheochromocytoma and paraganglioma

What is the best way of detecting and diagnosing these rare neuroendocrine tumours? Van Berkel and colleagues now present an overview of the latest evidence-based practice.

Tumoral secretion of catecholamines determines their clinical presentation, which can be highly variable among patients. Measurements of metanephrines in plasma or urine offer the best diagnostic performance and are the tests of first choice. Paying attention to sampling conditions, patient preparation and use of interfering medications is shown to be important, as these factors can significantly influence test results. When initial test results are inconclusive, additional tests can be performed, such as the clonidine suppression test.

Biochemical test results can also be used to estimate tumour size or to predict tumour location and underlying genotype. Furthermore, tumoral production of 3-methoxytyramine is associated with presence of an underlying SDHB (succinate dehydrogenase B) mutation and may be a biomarker of malignancy.

Read the full article in *European Journal of Endocrinology* 170 R109–R119 (OA)

Insulin secretion regulated by SIK2

Sakamaki and co-workers present a previously unknown mechanism for regulation of insulin secretion. Salt-inducible kinase 2 (SIK2) belongs to the AMP-activated protein kinase (AMPK)-related kinase superfamily. AMPKs are key regulators of metabolism, acting in the brain, liver, muscle, adipose tissue and pancreatic β -cells. SIK2 protein stabilises in β -cells by increased glucose levels, and is elevated in pancreatic islets of obese animals.

The authors have shown that β -cell-specific ablation of SIK2 reduces insulin secretion and glucose intolerance in mice, even when they are fed a healthy normal diet. When mice were challenged with a high-fat diet, β -cells from control animals responded by hypersecreting insulin; this effect was again limited in SIK2-deficient β -cells. In pancreatic islets obtained from obese mice, which compensate for the increased insulin demand by hypersecreting insulin, RNA interference-mediated loss of SIK2 abrogated the enhanced function of β -cells.

This research indicates that SIK2 signalling impacts upon β -cell insulin secretion and may constitute a pharmacological target for treating type 2 diabetes.

Read the full article in *Nature Cell Biology* 16 234–244

CLINICAL ENDOCRINOLOGY

Whole exome sequencing in pheochromocytomas/paragangliomas

McInerney-Leo *et al.* sought to assess whole exome sequencing (WES) in detecting germline mutations in pheochromocytomas/paragangliomas (PCC/PGL). WES was applied blind in subjects where mutations had already been found using a target gene sequencing approach.

Two different platforms were used to compare efficacy. In the first, WES identified six out of seven mutations, and, in the second, all mutations were found. Upon assessment of the capture efficacy of PCC/PGL genes, it was

found that the platform that had missed an SDHC mutation did not have adequate coverage for this particular gene.

The authors discuss pros and cons of WES versus Sanger sequencing. WES can have comparable efficacy in terms of finding mutations, provided that platforms with good coverage of all known PCC/PGL genes are used. WES also provides the opportunity to discover novel mutations, for which appropriate bioinformatics support is crucial. Last but not least, WES is considered a costly method, though this should become less of an issue in future.

Read the full article in *Clinical Endocrinology* **80** 25–33

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

High risk of thromboembolic episodes associated with thyroid storm

Min *et al.* report a 50-year-old man presenting acutely with confusion, shortness of breath and clinical features of thyrotoxicosis. He was diagnosed with thyroid storm, complicated by haemodynamic compromise due to fast atrial fibrillation and bilateral pulmonary emboli causing right heart strain. He received thrombolysis and care in the Intensive Therapy Unit. Thyroid function tests (TFTs) found thyrotrophin (TSH) <0.03mU/L, free thyroxine 71.4pmol/L, free triiodothyronine 27.4pmol/L, TSH receptor antibodies 38.2U/L. Carbimazole, i.v. steroids and low molecular weight heparin were employed and he survived this episode with normalised TFTs 1 month later.

Thyroid storm has a mortality rate of 10–20% and multiorgan failure is an independent predictor of poor outcome. Hyperthyroidism is associated with a hypercoagulable state; reports suggest a greater than twofold increase in the risk of pulmonary embolism affecting hyperthyroid patients. This can be even more pronounced in patients with severe thyrotoxicosis or thyroid storm. Therefore, anticoagulation (especially in the presence of atrial fibrillation) should be considered irrespective of the CHADS2 score.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* 2014 EDM130060

ENDOCRINE CONNECTIONS

Route of insulin administration affects the GH-IGF1 axis

Insulin-like growth factor 1 (IGF1) is synthesised in the liver following growth hormone (GH) receptor stimulation and is involved in growth and cell metabolism. Insulin may affect IGF1 bioavailability through the up-regulation of GH receptor expression and the down-regulation of IGF-binding protein 1 (IGFBP1) expression. In type 1 diabetes mellitus (T1DM), insufficient insulinisation of the liver may occur due to reduced insulin in the portal blood, potentially leading to dysfunction of the IGF1–GH axis.

Dijk and colleagues investigated whether continuous intraperitoneal (i.p.) insulin infusion, which facilitates higher insulin concentrations in portal blood, alters the

IGF1–GH axis in comparison with subcutaneous insulin administration. They found that serum IGFBP1 was significantly decreased during i.p. insulin infusion, suggesting the route of insulin administration is important for the IGF1–GH axis.

This indicates that additional benefits from insulin infusion could be derived by considering its route of administration. However, the clinical significance of the altered IGF1–GH axis in T1DM has not yet been fully characterised, so potential benefits derived from altering the route of administration require further investigation.

Read the full article in *Endocrine Connections* **3** 17–23



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Long non-coding RNA promotes aggressive prostate cancer

Prostate cancers are common, affecting 1 in 6 men, but are often non-aggressive. A few genes have been associated with aggressive prostate cancer, but the molecular basis for clinical heterogeneity between cancers remains poorly defined. Currently, hormone therapy is used, with the reduction of testosterone inhibiting tumour growth. A better understanding of tumour pathology will aid development of alternative therapies.

Prensner and colleagues report the involvement of a long non-coding RNA (named *SchLAP1*) in prostate cancer aggressiveness. *SchLAP1* was found in a subset of tumours, with expression associated with clinical progression and prostate cancer-specific mortality. Knockdown of *SchLAP1*, *in vivo*, reduced metastasis and tumour growth. Mechanistically *SchLAP1* antagonises the chromatin remodelling complex (SWI/SNF) resulting in dysregulated gene expression at numerous target genes.

Over the last few years, long non-coding RNAs have emerged as an extra component of gene regulation. The finding that *SchLAP1* antagonises a major epigenetic complex leading to an aggressive cancer phenotype has important implications for genetic regulation and cancer biology.

Read the full article in *Nature Genetics* **45** 1392–1398

Scent of goat hair: the new choice male pheromone

Goats have a very particular smell, which has now been identified as a novel, citrus-scented pheromone that directly activates the reproductive system in female goats. It was already known that it was the hair of males, not the urine, that demonstrated pheromone activity. Organic solvent extracts taken from male goat hair retained that activity, but a specific primer pheromone remained to be identified.



© 123RF STOCK PHOTO

Murata *et al.* focused on chemicals of that male hair essence, and particularly on the mostly unexplored neutral fraction. By using a custom-made goat head cap, the researchers collected scent synthesised by the head skin. Upon examining this scent they found 4-ethylctanal. This directly caused release of gonadotrophin-releasing hormone from female goat anterior pituitary. Furthermore, 4-ethylctanal oxidises to 4-ethylctanoic acid, a main ingredient of that 'goaty odour' known for decades for its role in attracting females to males.

Therefore, this research may have uncovered an innovative reproductive strategy on the part of the male goat to effect, through a single molecule, the behaviour and actions of the female reproduction centres for mating.

Read the full article in *Current Biology* **24** 681–686

SEX HORMONES: FROM 'ELIXIR OF LIFE' TO MECHANISM OF ACTION

WRITTEN BY IAIN J MCEWAN



*'Life is infinitely stranger
than anything which the
mind of man could invent.'*

ARTHUR CONAN DOYLE

(FROM THE COMPLETE ADVENTURES OF SHERLOCK HOLMES)

Open an endocrinology or cell biology text book and you will read a fairly accurate, if simplified, description of how steroid hormones act by binding receptor proteins that function as 'ligand-activated transcription factors'. However, the simplicity of this statement obscures the fascinating struggle and landmark discoveries that span more than a hundred years, and led to our current understanding of steroid hormone action.

CHEMICAL MESSENGERS

The late 19th century saw considerable interest in secretions from different organs that demonstrated powerful actions when administered to test animals or, in some cases, human guinea pigs. A leading practitioner in the embryonic discipline of endocrinology was the physiologist Charles Edward Brown-Séquard (1817–1894). He was an advocate of using tissue extracts to treat patients who showed signs of hormone deficiency. While his 'cure' for ageing was a placebo effect, it is now known that the testes, along with the ovaries, produce steroid hormones that have wide ranging actions.

FROM WASTE TO 'GOLD': THE ALCHEMY OF PURIFICATION

Today, it is perhaps difficult to appreciate the enormous effort that was required to purify the first steroid hormones: starting with thousands of litres of human or animal urine or kilograms of material from the abattoir. It is also hard to imagine the sense of achievement when a few milligrams of pure crystalline compound was finally seen in the flask.

The 1920s and 30s saw the successful isolation and ultimate chemical synthesis of the main classes of sex steroid hormones. The laboratories of A Butenandt (1903–1995) in Germany, and the USA's EA Doisy (1893–1986) and WM Allen (1904–1993) with GW Corner (1889–1981), led the way on work with androgens, oestrogens and progesterone respectively.

Following the isolation of steroid hormones, the next breakthrough saw the introduction of radiolabelled versions. Now researchers could trace where steroids ended up when given to test animals. Several laboratories realised that the radiolabelled hormone was enriched in the nuclei of cells in tissues, such as the prostate in the case of testosterone.

This completed an important part of the puzzle, and led Elwood Jensen to put forward the two-step model of hormone action. Previously, steroid hormones had been thought to work directly by interacting with the plasma membrane or by binding to and regulating enzymes in target cells. The Jensen laboratory proposed the presence of intracellular receptor proteins that translocated to the nucleus after hormone binding.

BIRTH OF THE NUCLEAR RECEPTOR SUPERFAMILY

In the 1980s, a number of groups in Europe and the USA, working independently or collaboratively, cloned the first steroid receptors: what is now oestrogen receptor α (ER α ; NR3A1) and the glucocorticoid receptor (NR3C1). The cloning of ER α was followed by the isolation of the cDNAs for the progesterone receptor (PR; NR3C3) and the androgen receptor (AR; NR3C4). In 1996, Jan-Ake Gustafsson and co-workers cloned a second receptor for oestrogens, which they called ER β (NR3A2).

Now, for the first time, recombinant technology could be exploited, producing large amounts of purified receptor domains, which in turn expedited the biochemical and structural analysis of the different receptors. The availability of the cDNA for steroid receptors also allowed a series of elegant studies delineating domain function.

MOLECULAR SIGNALLING MACHINES

Investigation of mechanisms of action also continued apace. In the absence of hormones, the sex steroid receptors can be mainly found in the cytoplasm (AR, PR) or partitioned between the cytoplasm and the nuclear compartments (ER α/β) in large multiprotein complexes with molecular chaperones (Hsp 90 and 70) and associated proteins. In the case of AR, there is good evidence that this complex maintains the receptor in a competent state to bind hormone. Once the hormone is bound, the receptors undergo a conformation change and are now predominantly in the cell nucleus, where they dimerise and bind to specific sites in the genome termed hormone response elements.

What happens once the steroid receptor is tethered to the DNA? Considerable research effort has gone into trying to answer this question. The DNA-bound steroid receptors can influence gene regulation in essentially two ways. In the first, the receptor directly recruits the transcription machinery to the target gene. In the second, the receptor recruits chromatin remodelling complexes, which use ATP hydrolysis or histone modifications to open or close the chromatin structure.

Although biochemically it is convenient to separate these functions, in reality the two mechanisms are likely to work in concert. Thus, once bound to DNA, the sex hormone receptors engage in multiple protein-protein interactions with co-regulatory protein complexes, which may function as co-activators or co-repressors.

Today, the identification of non-canonical DNA binding sites, the myriad of co-regulatory proteins and changes in epigenetic markers have all greatly increased our understanding of how sex hormones work, and also indicate the great complexity of hormone action. However, it is perhaps comforting to realise that the mechanism is still essentially Jensen's original 'two-step model', first proposed over 50 years ago.

IAIN J MCEWAN

Personal Chair in Molecular and Cellular Endocrinology,
University of Aberdeen

IT STARTED WITH A 'KISS'... HORMONAL CONTROL OF PUBERTY

WRITTEN BY JULIA K PRAGUE AND WALJIT S DHILLO



For a long time it has been known that the onset of puberty is the result of an intricate control of genetic factors and a number of environmental cues, including energy status and metabolic health, acting on the central pulse generator of gonadotrophin-releasing hormone (GnRH). However, it is only in recent years that the detail of such developmental events has been elucidated, with the further promise of novel therapies for conditions of reproductive dysfunction.

The onset of puberty is the final event of a transition whereby the amplitude and frequency of GnRH pulses sufficiently increase, having previously been quiescent in childhood after fetal and neonatal development. This is in response to reduced inhibitory and increased stimulatory tone on the GnRH neurones in the hypothalamus. In the subsequent cascade, the anterior pituitary is stimulated to release luteinising hormone (LH) and follicle-stimulating hormone (FSH), which act on the gonads to release sex steroids, resulting in pubertal development and gametogenesis. Two hormones have recently come to light from genetic studies of patients with idiopathic hypogonadotropic hypogonadism (IHH) and transgenic mice models: kisspeptin and neurokinin B.

IDENTIFYING KISSPEPTIN'S LEADING ROLE

The *KISS-1* gene encodes peptide products, collectively known as kisspeptins, which are cleaved to different lengths and activate the kisspeptin 1 receptor (KISS1R; previously known as orphan G protein-coupled receptor 54 (GPR54)). It was found that individuals (both human and mouse) with inactivating mutations in *KISS-1* or the KISS1R failed to enter puberty spontaneously. Further supporting evidence for the role of kisspeptin in puberty was confirmed with the demonstration that patients with activating mutations of the *KISS-1* gene developed central precocious puberty.

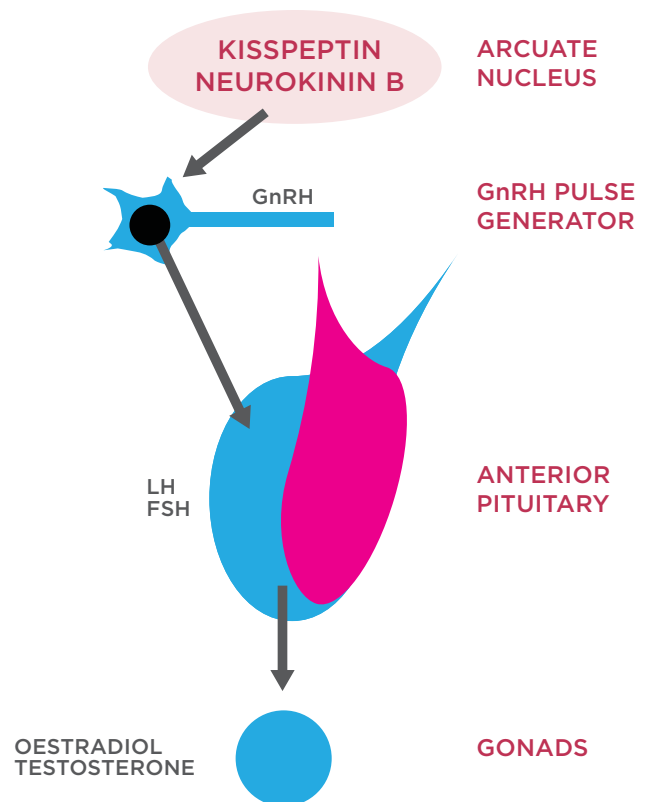
Subsequent studies have shown that kisspeptin acts above the level of the hypothalamic GnRH neurones to stimulate GnRH release, and subsequently a paradigm shift in our understanding of the regulation of the hypogonadotropic-pituitary-gonadal axis occurred.

Using similar studies of patients with less severe forms of IHH, other co-existing peptides such as neurokinin B (gene *TAC3*; receptor TACR3) have also been found to be important stimulators of the GnRH pulse generator. In fact, more recent evidence has shown that specific neurones of the arcuate nucleus, which project to the GnRH neurones, co-express kisspeptin and neurokinin B receptors.

THERAPEUTIC POSSIBILITIES

The discovery of kisspeptin in reproduction led to an explosion of research over the last 10 years. In animal models, it was shown that kisspeptin administration potently stimulated endogenous GnRH with subsequent gonadotrophin release. Clinical trials in humans have since consistently shown that infusion of kisspeptin, by either the intravenous or the subcutaneous route, stimulates the release of gonadotrophins in healthy men and women, as well as those with subfertility disorders including hypothalamic amenorrhoea. Kisspeptin therefore has potential as a novel therapeutic agent for patients with reproductive disorders.

Summary of the hypothalamic-pituitary-gonadal axis including anatomical position and probable effectors of the arcuate nucleus and/or GnRH neurones



PROBABLE EFFECTORS

- Nutrition/energy reserves (leptin, ghrelin)
- Metabolic health status
- Circadian signals
- Genetics (mutations, SNPs)
- Sex steroids

Furthermore, recent data suggest that single nucleotide polymorphisms (SNPs), as well as whole sequence mutations, are also important. In particular, using genome-wide association studies, polymorphisms of obesity-related variants have been identified as being related to the timing of menarche, and early menopause in some cases.

The identification of the genetic, environmental and biochemical factors that control puberty will undoubtedly lead to the discovery of yet more important and fascinating hormones and signalling pathways, which may also have potential as additional novel targets for our patients.

JULIA K PRAGUE
Postdoctoral Researcher, Imperial College London

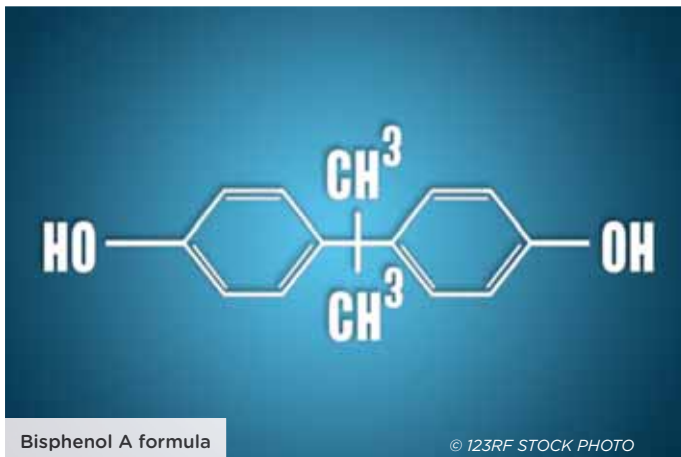
WALJIT S DHILLO
Professor of Endocrinology and Metabolism, Imperial College London

ENDOCRINE DISRUPTORS AND SEX: CONCERNS AND CONTROVERSIES

WRITTEN BY RICHARD SHARPE



Sex, or to give it its biologically correct title, reproduction, is all about hormones. Hormones establish sex (in males at least), and regulate its expression and its consequences. We could be forgiven for thinking that a romantic environment or alcohol is the primary driver of sex, but without the set-up by hormones, sex would literally not cross our minds.



Therefore, the notion that certain environmental chemicals, so-called 'endocrine disruptors' (EDs), could potentially interfere at one or more stages with 'sex' is inherently worrying, and incredibly newsworthy. The fact that we are all exposed to numerous EDs on a daily basis makes this an important issue for endocrinology and public health, as well as for us all personally.

POTENTIAL ROLE IN WESTERN DISEASE

There are numerous studies that associate human exposure to EDs with adverse health effects (obesity, insulin resistance, thyroid dysfunction, reproductive cancers), as well as effects on 'sex'. Taken at face value, one could argue that most common Western diseases could be attributable to ED exposure – and some scientists vociferously argue that this is the case. In reality, we do not know if EDs are even a minor, let alone a major, player in human disease, simply because of the difficulties in proving this one way or the other.

For example, exposure to the most talked about ED, 'bisphenol A', a very weak oestrogen, is significantly associated with numerous health disorders in humans. Is this causal or coincidental? A Western diet accounts for >95% of our bisphenol A exposure, and diet is also associated with the same disorders, so is bisphenol A simply a marker of calorie over-consumption? The fact that pharmacokinetic studies show that bisphenol A is rapidly inactivated within the body implies that it may be an innocent bystander. However, some would strongly disagree with this viewpoint. Whatever the truth, the fact that our exposure to the most important EDs (polychlorinated biphenyls, persistent chlorinated and fluorinated compounds, certain phthalates) is hugely affected by diet is a confounding factor that makes interpretation of association studies fraught with difficulty.

MALE REPRODUCTIVE DEVELOPMENT

But let's get back to sex. My main research interest is male reproductive health disorders, which can affect 20% of men and may be increasing in incidence. More and more evidence points to these disorders originating in fetal life, associated with suboptimal exposure to androgens during the critical short fetal 'masculinisation' period. For men, this androgen exposure is essential for making us what we are, so anything that interferes with fetal androgen production/action could cause adverse effects.

Numerous EDs with 'anti-androgenic' activity have been identified and, in animal experimental studies, these have been shown to cause one or more male reproductive disorders. Such studies invariably use doses far in excess of what we are exposed to, identifying a hazard but minimal risk. However, several groups have elegantly shown that if you combine much lower levels ('no effect dose levels') of up to ten EDs, then such mixtures potentially induce reproductive disorders in rats. Such studies get closer to the reality of our everyday ED exposures – low levels but lots of different compounds (a 'cocktail'). Other studies take this a step further by showing that exposure of male sheep *in utero* to 'our own exposures', via sewage sludge fertilisation of pastures, induces disorders of spermatogenesis in ~40% of males when they grow to adulthood.

Whether the sum of our exposure to relevant EDs is sufficient to interfere with fetal masculinisation in humans, and if so how common this is, are the big unanswered questions. Obtaining an answer is a Herculean task, considering the complexity of exposures to be measured and at what time (in the mother/fetus in early pregnancy). Clearly, the 'mixtures' issue also has wider relevance, as similar concerns about other EDs will apply (e.g. oestrogen-dependent female reproductive disorders). Therefore, concerns about ED effects on 'sex' remain an open and challenging issue for endocrinologists.

NON-MONOTONIC DOSE-RESPONSE RELATIONSHIPS

But let's finish on an even bigger challenge to endocrinology from the ED arena – non-monotonic dose-response relationships (NMDRs) and so-called 'low dose effects'. Essentially, this argument proposes that there is no threshold for ED effects, and that doses below the 'no effect' level may induce effects that are similar to those seen with higher doses. If this applied in endocrinology, surely we would have no menopause; hypothyroidism would cause similar effects to hyperthyroidism, and so on.

'Whether the sum of our exposure to relevant EDs is sufficient to interfere with fetal masculinisation in humans, and if so how common this is, are the big unanswered questions.'

The endocrine reality is that subnormal hormone levels result in different symptoms to supranormal levels. Moreover, how would negative feedback systems work if NMDRs applied? However, as many are convinced about NMDRs, it will remain a challenging issue for endocrinologists. My own perspective is that there are enough concerns about mixtures to keep us interested in sex without recourse to NMDRs!

RICHARD SHARPE
MRC Centre for Reproductive Health,
Queen's Medical Research Institute, University of Edinburgh

EUNUCHS, SOPRANOS AND SEX OFFENDERS: THE IMPORTANCE OF THE SMALL ORGANS IN HISTORY

WRITTEN BY PAUL GRANT



Farinelli (1705-1782) by Bartolomeo Nazari.
© Royal College of Music, London

The significance of the testicles was well recognised by ancient man. Damage to or loss of the testes as a consequence of accidental or purposeful trauma, or in the situation of diseased or undescended testicles, had important consequences. It could result in lack of development of secondary sexual characteristics (becoming a man), or loss of fertility, sexual drive and sexual ability, as well as changes in bodily appearance.

The role of the testes was also well recognised in theories of conception. The effect of castration in animal husbandry was put to good use when turning wild animals into domesticated ones and making them more suitable for the purposes of man.¹

CONTROL, PUNISHMENT AND RELIGION

Castration had been practised on a large scale for centuries, not only to control slaves and as a punishment for defeated warriors, but also in certain religious orders (to control lascivious thoughts among the priesthood) and for the male attendants of harems. Interestingly, it would appear that there was a spectrum of human castration. In the history of eunuchs, it was possible to have married eunuchs, eunuchs in harems or those in the order of Imperial Rome who had love affairs of sorts and were sought after by women as there was no danger of pregnancy. Eunuchs also tended to feature prominently in the civil services of the Chinese, Byzantine and Roman empires. Some even excelled as generals.

SUFFERING FOR ONE'S ART

Castrati (men castrated as choirboys) were famed in more recent times as singers of extraordinary power and range, given the lack of pubertal laryngeal maturation. At the height of the craze for male sopranos, 5,000 boys a year were castrated in order to preserve their unbroken voices. In the absence of anaesthetic, boys were doped with opium and bathed in milk before having their testicles removed by slitting the groin and severing the spermatic chord.

Those who survived were tall, beardless and tended to run to fat. They also had no Adam's apple (the famous 18th century castrato Farinelli, pictured above, wore a tactical cravat) and their voices did not break. Those who proved mediocre mouldered away in parish choirs, but the successful 'sacred monsters' were cosseted and adored. The last official castrato, Alessandro Moreschi, retired from the Sistine Chapel in 1913.

IN MODERN TIMES

Chemical castration has been used in more modern times as an intervention to reduce arousal, libido and sexual activity, and involves the use of anti-androgen drugs, Depo-Provera or even anti-psychotics such as benperidol. It has been used as part of treatment for psychological disorders, but also as a means of public or judicial policy for behavioural control in sex offenders (as a 'humane' alternative to long term imprisonment), despite concerns over human rights and possible long term side effects.

California was the first state in the USA to specify the use of chemical castration as a punishment for child molestation, following the passage of a modification of the penal code in 1996. This law stipulates that anyone convicted of molestation with a minor under 13 years of age may be treated with Depo-Provera if they are on parole after their second offence, and that offenders may not refuse the treatment. In the UK, Alan Turing, famous for his contributions to mathematics, computer science and code-breaking, was a homosexual who chose to undergo chemical castration in order to avoid imprisonment in 1952.

LUMPS AND BUMPS

Hernia, which comes from the Greek for 'bud' or 'offshoot', has long been recognised as a structural complication of the testicles. Most essential knowledge concerning hernias in ancient times derives from the Greek physician and philosopher Galen, who lived in Rome. English surgeon Astley Cooper, working in the early 19th century, stated that 'no disease treated surgically involves from the surgeon so broad knowledge and skills as hernia repair and its many variants'. The introduction of anaesthesia and antiseptic procedures constituted the beginning of modern hernia surgery, known as the era of hernia repair under tension (from the 19th to mid-20th century).

SEMINAL CONCLUSIONS

So what have we learnt about the 'orchids'? First, we appreciate that they are an important source of manhood and fertility, and that endocrine failure can lead to a wide range of metabolic and psychosocial issues. Secondly, it is clear that the neutered male can have both artistic and important social roles by removing the interference of sexual maturation and desires. In addition, hormonal manipulation can be used to control 'deviant sexual behaviours'. Finally, it seems that structural compromise of the testicles has been recognised for many thousands of years, but it has only been with the last 100 years or so that surgical techniques have developed sufficiently to correct the problem and avoid recurrence.

PAUL GRANT

Consultant Endocrinologist,
Royal Sussex County Hospital, Brighton

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DISORDERS OF SEX DEVELOPMENT: NEW CONCEPTS AND CONSIDERATIONS



WRITTEN BY FAISAL AHMED

Whether we develop as men or women is one of the most profound illustrations of how biology influences us as individuals, affecting our daily actions, including how we think, how we behave, the choices we make, the opportunities we have and our long term health outcome.

Given the wide implications of this binary alternative, it is even more remarkable to imagine that this switch in our development critically depends on whether the mother's egg was fertilised by an X or a Y chromosome-bearing sperm. The chain of events that are set off after this step leads to the development of testes or ovaries as well as male or female reproductive organs and genitalia.

THE FATE OF THE GONAD

Whilst, superficially, the fate of the gonad seems to be solely determined by the chromosomal complement, the description of the *SRY* gene as the critical testis determining gene, the subsequent discovery of a number of genetic factors that control testis and ovary development and, in addition, the identification of several people with a range of conditions affecting gonadal generation have clearly shown that gonadal development and maintenance is a complex process that needs further study. The concept of gonadal maintenance, where gonads that may initially function adequately may be at risk of early degeneration, is, itself, relatively novel in the field of disorders of sex development (DSDs) and highlights the need for long term monitoring of gonadal function.

PUSHING THE BOUNDARIES

NR5A1 is a gene coding for steroidogenic factor 1, a transcription factor controlling the activity of several genes related to gonadal and adrenal development. It is clear that mutations in such genes can present with phenotypes ranging from XY complete gonadal dysgenesis through to XY partial gonadal dysgenesis, XY male infertility and XX ovarian failure. Whilst emphasising the critical nature of this gene in gonadal development, this also highlights the clinical benefit of identifying this genetic cause and the need for improving the diagnostic capability of our medical genetic services.

The wide variation in phenotype within a single genetic disorder also highlights potential conflicts that may exist within the DSD classification which was created almost a decade ago. DSDs were defined at that point as any congenital condition in which development of chromosomal, gonadal or anatomical sex is atypical, and the classification was developed to encompass this definition and was based on aetiology. The debatable question now is whether the DSD classification should be flexible enough to include conditions such as primary ovarian failure and male infertility.

DIFFERENCES VS DISORDERS

This appreciation of the widely variable phenotype that may be associated with a disorder of a single gene is not new. This has been known for the androgen receptor for a number of years, where mutations in *AR* can be associated with a range of X-linked conditions including XY complete androgen insensitivity syndrome as well as partial androgen insensitivity syndrome. What is even more interesting and thought provoking is that some mutations and variations in the length of polyglutamine repeats in *AR* may be associated with conditions such as male-pattern baldness in men, which this author, at least, does not consider to be a disorder! This raises the issue of the reasoning behind referring to a condition linked to a genetic variation as a disorder or a difference. Whilst I may not consider male-pattern baldness a disorder, it is clear many perceive this condition as a disorder which requires treatment.

STEROID BIOSYNTHESIS IN 3D

Recent advances in our knowledge in the field of DSDs that have challenged traditional concepts have not simply been in the field of genetics, but also in our understanding of steroid biosynthesis. Just when most 'mature' endocrinologists felt comfortable with the diagram on their office wall, it is becoming clearer that what they need is not a 2D illustration of the biosynthetic pathways but a 3D figure, which can provide a better understanding of concepts such as the testosterone-independent backdoor pathway for dihydrotestosterone synthesis. This highlights an intrinsic weakness of a pathway-driven body of knowledge such as endocrinology, where most learning and teaching have occurred in two dimensions, but where concepts may be easier to understand if illustrated in an additional third dimension.

AND BACK TO 2D

The two dimensional concept of being male and female is core to the area of sex development. However, do we really all agree on what constitutes being a boy or girl, man or woman? These are difficult concepts to generalise, given that there will be strong cultural, societal, temporal and geographical influences on the thinking of any individual person as well as the society in which they exist. When concerns exist about a person's sex development, the concepts of gender and the biological features that are conventionally associated with one's sex need to be deconstructed in the context of that specific person. This can only be effectively performed by a team of clinical experts with complementary skills.

FAISAL AHMED

Samson Gemmell Chair of Child Health, University of Glasgow and the Royal Hospital for Sick Children

The official Society for Endocrinology guidance on the initial evaluation of an infant or adolescent with a suspected disorder of sex development can be downloaded free from our website at <http://bit.ly/1fdizvv>.

'DSDs were defined as any congenital condition in which development of chromosomal, gonadal or anatomical sex is atypical ... The debatable question now is whether the DSD classification should be flexible enough to include conditions such as primary ovarian failure and male infertility.'

TAKE CARE OF YOUNG PEOPLE (AND DON'T FORGET TO TALK ABOUT SEX!)

WRITTEN BY ROHANA J WRIGHT & HELENA K GLEESON



'Caring for young people is everybody's business' – so reads the first key message regarding adolescent healthcare in the recently published Chief Medical Officer (CMO)'s Annual Report for 2012.¹ It has highlighted the importance of working to improve outcomes in young people with long term conditions.

In endocrinology in the UK, there is evidence that our outcomes need to be improved, with reports of increased mortality in women with Turner syndrome² and that young people with congenital adrenal hyperplasia become lost to follow up around the time of transfer from paediatric to adult services and fail to engage with adult care.^{3,4} We also need to think about young people beyond their condition (noting the facts about their sexual health, as shown in the inset).⁵

CURRENT ADOLESCENT HEALTH TRAINING

A recent survey of adult and paediatric higher specialist trainees in endocrinology was undertaken to elucidate training needs and whether they are being met. Preliminary results suggest that a multitude of training needs are unmet in this area. A total of 60% of trainees felt that training in adolescent health and transition was minimal or non-existent. This is more of a problem in endocrinology than in diabetes: three-quarters of trainees reported a deficiency in adolescent endocrinology training compared with 39% in adolescent diabetes.

Trainees reported lack of clinic exposure and formal training as contributing factors. Another common deficiency is experience in dealing with non-medical issues, including psychosocial factors, education and employment. Only a quarter of trainees reported satisfactory training in these areas. For example, only 40% of diabetes and endocrinology trainees have received training in sexual health, and 69% rated this as a training need as 3 to 5 out of 5.

Currently the JRCPTB (Joint Royal Colleges of Physicians Training Board) curriculum lists several detailed competencies regarding the care of young people with diabetes, but few in endocrinology. These cover medical, social and psychological aspects, as well as the importance of reflecting on our own behaviour when dealing with young adults and adolescents. However, the list of competencies is not comprehensive. For example, no mention is made of sexual health, and there is no guidance about how they can be effectively achieved or measured.

SEXUAL HEALTH IN YOUNG PEOPLE TODAY⁵

1. The average age of first heterosexual intercourse is 16 years.
2. Among women aged 16–49, the lowest levels of contraceptive use are found in those aged 16–19 years.
3. Two-thirds of 16- to 19-year-olds are 'at risk' of pregnancy (i.e. have a sexual partner); approximately one in ten of those with a partner do not use contraception.
4. 2011 saw the lowest rate of conception among those aged under 18 since 1969, but the UK still has a relatively high birth rate among 15- to 24-year-olds compared with other countries.
5. The highest rates of sexually transmitted infections are among people aged 15–24 years. Those under 25 accounted for 64% of all new *Chlamydia* diagnoses in 2012.

CONCERNS VOICED IN TRAINING

'Transition and adolescent medicine do form part of the diabetes and endocrine curriculum, but as a trainee, I have had very little exposure to this area, and this gap in my training means that I feel under-prepared to meet the specific needs of this group of patients.'

'I am concerned that lack of training is a contributing factor to why many young people are lost to follow up at this crucial time in the management of their chronic condition.'

'We have almost no opportunities to get training in transition medicine and very limited opportunities to get experience in adolescent medicine.'

MAKING IMPROVEMENTS: THE RCP STEERING GROUP

The CMO's report calls for adult long term condition strategies, age appropriate facilities and high quality transition. However, for these to be delivered effectively, training is required. The Young Adult and Adolescence Steering Group at the Royal College of Physicians (RCP) is attempting to begin to improve training, with a plan to survey trainees across all medical specialties to appreciate the extent of the training problem, in order to help drive change and find solutions.

In addition, the Adolescent Health Project⁶ is an e-learning resource, developed by the Royal College of Paediatrics and Child Health and e-Learning for Healthcare, which can complement the clinical resources accessible to trainees locally. Personally, we feel it can strengthen communication skills with young adults, gives a greater appreciation of the complexities of this period of life, and increases confidence in dealing with some of the challenges surrounding adolescence, including talking about sex. Whilst this does not replace clinical exposure, it has definitely added to our experience in young adult and adolescent medicine.

Hopefully, the efforts by the RCP Steering Group will go a long way towards changing the future landscape for the care of young people in adult endocrinology.

ROHANA J WRIGHT
Royal Victoria Infirmary, Newcastle upon Tyne

HELENA K GLEESON
Leicester Royal Infirmary, Leicester

If you are interested in this area of endocrinology and working towards improving training please contact the authors via endocrinologist@endocrinology.org

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GENDER REASSIGNMENT IN 2014: MOVING ON FROM THE DARK AGES?

WRITTEN BY LEIGHTON SEAL



Poor quality research due to small sample sizes and short follow up times has hampered the field of gender reassignment. The result has been a plethora of approaches to the hormonal treatment of gender dysphoria. Choosing the best protocol has therefore been difficult, especially as many studies are conducted in the USA or Europe where the cost of medicines is important in deciding which drugs to use.^{1,2}

However the situation is now improving. Recent studies have attempted to compare different treatment approaches,³ and two publications have shed light on the long term outcome of treatment for gender dysphoria,^{4,5} providing us with actual data on which to base our practice.

OESTROGEN THERAPY IN TRANSWOMEN

The hormonal treatment of transwomen (male to female transitioners) is effective and safe. However, the major risk of oestrogen therapy, as in natal females, is thromboembolism. In the past, conjugated equine oestrogen in combination with cyproterone acetate was commonly used, with the risk of deep vein thrombosis (DVT) reported as 20 times background (2.8%).⁶ This resulted in a move to topical oestrogens in Europe. However, my own group has recently demonstrated that premarin has a DVT rate eight times higher than oestradiol valerate, suggesting that it is the type of oestrogen, not the route of administration, that is important in reducing DVT risk.³ We use doses of oestradiol up to a maximum of 10mg per day, with a DVT rate of 0.5%.³

Current data suggest that long term treatment with oestrogen in transwomen is associated with a slight increase in the standard mortality ratio. The increase in mortality appears to be associated with an increase in risk of suicide in vulnerable individuals [hazard ratio 5.7⁵ 19⁴] and also in cardiovascular deaths [relative risk 1.46⁵ 2.5⁴].

The increase in suicide deaths appears to be historical when comparing the cohort treated in 1972–1980 with that in 1983–2010.⁴ This may reflect improvements in the availability and quality of care or alternatively improvement in the status of transpeople in society, leading to a reduction in their psychological stress. However, it is important that the psychological health of people treated for gender dysphoria should be assessed.

The increase in cardiovascular disease appears to be associated with the use of ethinyloestradiol but not other oestrogen types, so this oestrogen type should be avoided.⁵ Breast cancer is extremely rare in transwomen and equates to the background breast cancer risk in males, therefore hormone treatment can be lifelong.⁷

TESTOSTERONE SUPPRESSION

The traditional anti-androgens used for testosterone suppression, such as spironolactone and cyproterone acetate, have a plethora of side effects, including depression (a common psychological comorbidity in people changing their gender).^{3,8} Recently, we found that individuals using spironolactone were more likely to need breast augmentation in the longer term, suggesting this drug prevents adequate breast development.³ For these reasons there has been a switch in UK practice to using gonadotrophin-releasing hormone analogues as standard for testosterone suppression.⁹

FEMALE TO MALE TRANSITION

Current data suggest that long term treatment with testosterone in transmen (female to male transitioners) is not associated with any increased risk of cardiovascular disease. The standard mortality ratio of this patient population is 1 (i.e. there is no increase in mortality).^{4,5} Factors associated with lifelong hormonal therapy and the target levels for hormone replacement are the same as for the general male population.

If patients retain their uterus, then standard cervical screening programme recommendations should be followed, with an endometrial ultrasound every 2 years to monitor for endometrial hyperplasia.^{2,9} The patient should be advised that they will not get an automatic call up for smears once their gender has been changed, and they will need to remember to have this done in either a primary care or sexual health clinic setting. Even if the patient has mastectomy and male chest reconstruction it is important for them to realise that some breast tissue will remain and they should continue with self examination.

TRENDS AND TRAINING

The incidence of people presenting to gender services is increasing rapidly at our own clinic. The case load appears to double every 5 years and we have about 4,500 patients being actively assessed. This equates to an estimated incidence of between 1:7,440¹⁰ to 1:30,000 for birth gendered males and 1:10,000 to 1:31,153¹⁰ for birth gendered females, making this a relatively common disorder.

After assessment is complete, individuals are currently discharged back to local services, so more and more patients will be seen in endocrine clinics seeking advice on how their hormones should be managed. Consequently, the cloud on the horizon is the need for training. Last year saw publication of the *Good Practice Guidelines for the Assessment and Treatment of Adults with Gender Dysphoria* as a Joint Royal Societies guideline.⁹ This is a good basis for practice, but not a substitute for organised clinical training, which is absent from both medical school and specialist training curricula – an area where the Society for Endocrinology could take a lead.

LEIGHTON SEAL

Consultant and Honorary Senior Lecturer in Endocrinology
West London Mental Health Trust and St George's Hospital London

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TESTOSTERONE REPLACEMENT IN MEN: BACK TO THE FUTURE

WRITTEN BY RICHARD QUINTON

'In the best interests of medical science, we write to recommend retraction of the article by Vigen et al.¹ The study is no longer credible ... we urge you to retract this article immediately.'

So read a recent request to the Editor-in-Chief of *JAMA* from The Androgen Study Group and others.² This co-ordinated post-publication assault on a medico-scientific publication is unprecedented, in my memory at least, and reflects the degree of fear and loathing aroused among a particular faction of US physicians, comprising largely non-members of the Endocrine Society. Hell certainly hath no fury like a physician fearing for his (they generally are men) livelihood and clinical reputation. So how did we come to this situation that echoes over a decade of controversy in relation to postmenopausal hormone replacement in women?

THE ADAM SCORE

Do you lack energy? Are you sad and/or grumpy? Are you falling asleep after dinner? Have you noticed a recent deterioration in your ability to play sports (step forward most of the Manchester United football team)? Has there been a recent deterioration in your work performance? Have you noticed a decreased enjoyment of life?

Did you answer 'yes' to even three of these seven earth-shatteringly specific questions contained in the ADAM (androgen deficiency in ageing males)³ score? If so, you may have 'low testosterone' and should ask your doctor for a serum testosterone check, because (even if you answered 'no' to two further questions enquiring after defective libido and erections), you may benefit from testosterone replacement therapy (TRT) – or so the story goes.

ADAM's inventor recently admitted that (I kid you not) he had devised it during a particularly inspirational bathroom break that yielded him some \$30,000 in pharma research-funding.⁴ Yet vast numbers of American men have started TRT entirely on the basis of this kind of clinical screening *without a baseline serum testosterone check*⁵ and there has been an explosion in annual testosterone prescribing in the USA (\$3 billion and nearly 3 million men filing scripts, amounting to a tenfold increase over the past 10 years). The UK is beginning to show a similar trend even without the 'rocket fuel' of direct-to-consumer advertising.⁶

SERUM TESTOSTERONE SCREENING

For the record, serum testosterone should only be screened when fasted at 08.00–10.00 in otherwise healthy, well-rested men, with a reasonable pre-test probability of being hypogonadal. This is because of the circadian rhythm in gonadotrophin-driven testosterone secretion and the reversible fall in serum levels described with acute glucose-loading and all known physical, psychiatric, acute and chronic disease states.⁷

So nobody would have been surprised to discover a direct relationship between high serum testosterone, as a biomarker of male health, and longevity. However, a recent longitudinal study of community-dwelling older men found the best outcome accrued to men in the second quartile for serum testosterone, rather than the top one (the worst predictably accrued to those in the bottom quartile).⁸ The very highest serum levels may be associated with prothrombotic effects, possibly mediated through higher haematocrit.

WHAT ROLE FOR REPLACEMENT?

Nevertheless, the possibility that TRT could have a positive disease-modifying action in men with age-related frailty and chronic diseases has attracted much interest. Indeed, lots of translational research and even a very sound (though slightly under-powered) clinical trial⁹ have tended to support the use of TRT in this cardiometabolic role. In the context of so much uncertainty, clinicians would be well-advised to read the Society for Endocrinology's pragmatic and measured position statement.¹⁰

Several recent publications have not only reinforced the need for caution in TRT for men without classical organic hypogonadism, but have also drawn the attention of both of the US Food and Drug Administration (FDA) and at least one American law firm sniffing a potentially lucrative class action.¹¹ First, a clinical trial of TRT in men with age-related frailty had to be terminated early due to an excess of cardiovascular events.¹² The same worrying cardiovascular event signal was also captured by a recent meta-analysis of randomised controlled trials¹³ and by two recent American 'database-crunching' studies.¹⁴

We don't yet know the likely form of the FDA's investigation. It may choose to await the outcome of the National Institute of Aging's prospective study of TRT in about 800 symptomatic, older men with unequivocally low testosterone. Peter Snyder, the lead investigator has already stated that the study isn't powered to detect adverse morbidity/mortality outcomes; only to capture potential benefits. A surer way forward would be to make the licenses of testosterone products (to treat men outside narrowly defined criteria of classic hypogonadism) contingent upon funded commitments to prospective clinical trial data, or at the very least, large-scale recruitment to long-term patient registries. Where the FDA goes, the European Medicines Agency is likely to follow, but we should meanwhile be requesting the resumption of pharma support to the RHYME registry,¹⁵ which was prematurely closed due to a funding shortfall.

RICHARD QUINTON

Institute of Genetic Medicine, University of Newcastle on Tyne and Newcastle Hospitals Foundation NHS Trust

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TALES OF THE UNERECTED

WRITTEN BY ANGELA GREGORY

Men name it, compare it, find it comforting, play with it, admire it, and it makes them feel like men.

But, when it doesn't work... THEY WORRY ABOUT IT!

For the past 14 years as a sex therapist, I have shared the worries, anxieties and notions men have about their penis. Men hold fantastical beliefs about their manhood. Older men cannot understand why 'it's not like it used to be', to which I regularly remark, 'no Mr B it isn't, and that's because neither is the rest of you'. Younger men seem to expect that it should work regardless of how many pints they have consumed, how attractive they find their partner, how many times that week they have masturbated or how much porn they have viewed.

A PROBLEM OF MIND OR BODY

Generally speaking, men are 'solution focused', so when their penis doesn't perform, they spend inordinate amounts of time trying to find a reason why. When they eventually admit defeat and go and see their GP, they will insist that the poor unsuspecting doctor comes up with a medical reason for its lack of vitality. There seems to be a commonly held belief that if a medical reason can be identified, it can be treated and their most prized possession will return to its former potency – and a complete lack of awareness that a diagnosis of cardiovascular disease or diabetes will mean that a medically induced manhood is the best they can hope for.

However, if a medical reason cannot be found, and a man is told his problem is likely to be psychogenic, you're likely to have a confrontation on your hands. You need to be very brave to challenge his insistence that he hasn't got performance anxiety or lost his confidence. But it can be helpful if you give him an explanation, and enlighten him about the effects of adrenaline, and how worrying and relying on sheer willpower is enough to cause or maintain an erection problem. This can even interfere with the effectiveness of whichever PDE5 inhibitors are prescribed. Even men diagnosed with an organic disease will have a psychogenic component, as I have yet to meet any man who isn't concerned about his loss of manhood.

RESENTMENT IN RELATIONSHIPS

The penis has a starring role in sex, a suitably rigid erection begins penetration and ejaculation ends it. In essence, the penis can get stage fright regardless of aetiology. The longer a sexual problem goes unidentified and untreated, the greater the potential impact on the couples' relationship. Avoidance of sexual contact is common. The man stops initiating, in case his penis doesn't stand to attention at the desired moment, and his partner either doesn't want to pressure him or feels angry and resentful that he runs for the hills at the first sign she is feeling frisky. What he doesn't do is explain that his penis has become the enemy and he doesn't want to put himself in a situation that makes him feel humiliated.



Men also complain that their penis looks smaller, to which the gentle response should be that it is a question of perspective related to abdominal obesity rather than penis size. Losing weight will make the penis look bigger and cardiovascular exercise will improve circulation, which in turn will help erectile responses: a marketing dream for promoting a healthier lifestyle.

The avalanche of internet pornography is also having an impact on men's functioning, and I now ask men 'how often do you masturbate?' rather than 'do you masturbate?'. One retired gentleman, referred by his GP with erectile dysfunction and delayed ejaculation, described masturbating daily with pornography, for up to 2 hours. Basically he had desensitised himself to 'normal' sexual arousal, and one of my early treatment interventions was to suggest rather diplomatically that perhaps he should consider getting an allotment!

AN EARLY INDICATOR OF ILL-HEALTH

In today's NHS, treating erectile dysfunction is often seen as trivial and sex as a recreational activity. However, the penis is a body part and a lack of erections is an early warning sign of ill-health. Men with erectile dysfunction will often lose morning and night time erections as well as those for sexual function. Night time erections are a way of taking oxygenated blood to the penis, so the longer a man has a lack of erections the more this will impact not only on how he feels and on his relationship, but also on the endothelial function of his penis. What other body part would we ignore if it wasn't getting the blood flow it needed?

Treating erectile dysfunction restores the man and his relationship. The pride and joy of a man able to function again can be something to behold and, with the advent of modern technology, I am sometimes subjected to full colour high definition photographs of man's most prized possession, to which I generally remark, 'well Mr X you must be very proud' – although I find it difficult to see with any clarity without my glasses on!

ANGELA GREGORY

Angela Gregory is the Lead for Psychosexual Therapy at the Chandos Clinic, a sexual dysfunction service for men and women at Nottingham University Hospital Trust. She has worked as a full-time Sexual and Relationship Psychotherapist for the past 14 years. She provides in-house training for both medical and nursing staff and regularly lectures at a national level.



A TIME OF CHANGE, A TIME FOR CONSENSUS: MENOPAUSAL HORMONE THERAPY

WRITTEN BY NANETTE SANTORO



The 2002 publication of the principal findings of the Women's Health Initiative (WHI)¹ led to greatly diminished enthusiasm for the use of hormone therapy. It has been estimated that prescriptions dropped by 50–60% in the USA, and in many other developed countries that had previously practised widespread use.

Initial reactions to the WHI by our European colleagues can be summed up by the following statement from Women's Health Concern UK: 'The women studied in the WHI were North American women in their mid-60s, often overweight and thus totally unrepresentative of women in the UK for whom hormone replacement therapy might be considered suitable.'²

Hmmm. The assumption that North American women are overweight and UK women are not is not substantiated by current data. The mean BMI of women in the USA is 28.5kg/m², compared with 26.9kg/m² in the UK.³ For a woman who is 5'4" tall, this is the difference between weighing 166lbs and 157lbs. It seems we are getting closer in mean BMI on the two sides of the Atlantic Ocean. Unfortunately, this is not because Americans are getting thinner.

'Menopause still seems to be viewed as a hormonal deficiency syndrome in the UK, where treatment is often referred to as "hormone replacement therapy" rather than "hormone therapy"'

The second major concern cited about the WHI was that the participants were far beyond the age at which hormone therapy would be initiated. Most women would begin hormones at the time of menopause, in their late 40s or early 50s, and thus it seemed preposterous to initiate a study of hormone therapy when women were in their 60s and 70s. Yet, prevailing wisdom in the 1990s was to continue the treatment indefinitely, as long term health benefits appeared likely. Many women took hormones well past the interval of time when their symptoms would have justified their use.

The subsequent findings of the Million Women Study (MWS),⁴ published a year later, supported the WHI's finding of an increased risk of invasive breast cancer in women taking oestrogen plus progestin (E+P), now in a UK population. Assumptions that the 'American progestin' (medroxyprogesterone acetate) or characteristics of American women that made them uniquely susceptible to breast cancer were the chief causative factors in the increased breast cancer risk observed in the WHI became untenable when the MWS indicated a very similar magnitude of risk (small, but progressive) in women taking other E+P regimens.

The MWS also reported, somewhat contrary to the WHI, that E-alone regimens were also associated with an increased risk of breast cancer, albeit smaller than with combined E+P treatment (hazard ratio 1.30 [95% CI 1.21–1.40] for E-alone compared with 2.0 [95% CI 1.88–2.12] for E+P). Paradoxically, the WHI E-alone trial found an initial decrease in breast cancer risk in women who had had a hysterectomy and took conjugated equine oestrogens,⁵ and this decrease has persisted throughout prolonged follow up.⁶

The world has since moved towards consensus, and this is good for women. The most recent summary of the findings of the extended post-stopping phase of the WHI examined all of the original health outcomes over active treatment (5.6 years for E+P and 7.2 years for E-alone) with 13 years of cumulative follow up.⁶ When broken down into 10-year age groups at randomisation, there is great uniformity in the relative risks and benefits of hormones, and very few isolated conditions where the hormone intervention resulted in a statistically significant association with a disease outcome. There were also few outcomes that differed greatly by age at initiation of hormones.

There remain a few small discrepancies between medical practice in the USA and the UK that bear mention. Overall, non-hormonal alternatives for menopausal symptoms do not appear as popular in the UK as in the USA. Testosterone is available to women in the UK, but not in the USA. Menopause also still seems to be viewed as a hormonal deficiency syndrome in the UK, where treatment is often referred to as 'hormone replacement therapy' rather than 'hormone therapy'.⁷

Finally, the 'bioidentical hormone' movement that has had such a large media presence in American practice is a bit more muted in Europe. One physician's website sarcastically proclaims, 'There seems to be a widely held view that the use of bioidentical hormones is a clever recent American development that is a vital advance on orthodox hormone replacement therapy'.⁸

But then again, it seems that the UK is not without some evidence of a 'Suzanne Somers' factor (Somers is a high profile celebrity supporter of the approach in the USA). One UK website declares, 'Bioidentical hormones are able to produce all the desirable effects of hormones with far fewer side effects, simply because they are biologically identical to our natural hormones already produced by our bodies'.⁹

Taken together, short term use of menopausal hormone therapy for symptom treatment is a very reasonable intervention and, thanks to a great deal of high quality research on both sides of 'The Pond', we know a lot about how it is likely to help and/or cause harm. Numerous consensus statements have been published on the risks and benefits of hormone therapy for symptomatic menopausal women, and international agreement seems to now be the rule.¹⁰

NANETTE SANTORO

Professor and E Stewart Taylor Chair of Obstetrics & Gynecology,
University of Colorado School of Medicine, Aurora, CO, USA

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SEEDLINGS

FROM OUR SCIENCE COMMITTEE CORRESPONDENT

Through repeated necessity, I have got better at dealing with rejection letters. However, the first cut is the deepest, and a letter from the *Student BMJ* in 1993 still holds bittersweet memories.

'Dear Mr Coll, Thank you very much for your review article outlining the biochemical actions of lithium. Although it is a comprehensive piece it is too complex for our audience.'

That's it? Outrageous! I had even come up with a pithy title 'Lithium in psychiatry: an ion taming act' and had *hand-drawn* a figure depicting how lithium disrupts inositol metabolism.

My lost masterpiece was written during a placement at the Institute of Psychiatry. Initially kept to be revised and sent elsewhere, it got swept up in boxes labelled 'to sort'. What saved it when it resurfaced were the exquisite pencil annotations that had been carefully added to the margins. When I wrote it, I was supervised by a stellar cadre of inquisitive clinician scientists who were palpably excited about what they did. One took the time to read, correct, add further references and hand-write encouraging notes all over my text, when he could easily have quickly thumbed through and signed the bottom. This modest act was a huge boost for me at the time.

Over the last few years, our department has become increasingly vexed about how to attract basic scientists and clinicians into endocrinology. We seemed to be losing out to the gravitational pull of other specialities,

with misrepresentation of what 'clinical metabolism' actually involves also effectively repelling anyone with another viable career option.

To save us from our introspective misery, out popped an acid green shoot in the form of a message from a student who was fed up of her lack of exposure to endocrinology and wanted more! A few encouraging emails and coffees later, we had an inaugural meeting. Sixty students came to hear four speakers giving the talks they all would wish to give were it not for crowded timetables. We've since had an old school debate on the merits of metabolic control in hospital. There was a visible unfolding within the participants that this stuff might actually matter – that it was important and relevant.

My old lecturer's efforts on a rinky dink essay could have been judged foolish, as at the time they went unrewarded, unpublished, unthanked. However, enthusiasm is infectious and it does not require a huge titre to make it transmissible, particularly if an individual has not been exposed to it for a while. Paddling in nostalgia never did much for anyone, but rediscovering and cultivating what first thrilled us about the subject is a pointer to fixing the future.



TONY COLL
Science Committee member

COMMISSIONING IN ENDOCRINOLOGY

FROM OUR CLINICAL COMMITTEE CORRESPONDENT

As reported in *The Endocrinologist* (issue 108), NHS England has set up around 75 clinical reference groups (CRGs) for different specialty areas. CRGs have clinical representatives from all over England, together with stakeholders including patients and pharmaceutical companies. The initial aim of the Specialised Endocrinology CRG was to produce a specification for highly specialised conditions in endocrinology. Wide consultation was carried out.

The service specification is not set in stone and will be updated regularly. It does not delineate the centres that will carry out particular services, but the team members needed to provide high quality care for patients with specialised endocrine conditions. Networks of referral and care provision are largely established but these will be consolidated.

The CRG aims to implement the specification flexibly according to local needs. Improved quality of outcome in endocrine surgery should be achieved by ensuring sufficient experience and that adequate numbers of patients are operated on in particular conditions. Pre- and post-surgical care will remain with the referring centre according to local pathway agreements.

I regard the CRG as an excellent opportunity for clinical endocrinologists to define and run endocrinology across England for the first time, but there are issues.

1. CLINICAL CODING

Currently individual outpatient attendances are not individually coded and so it is impossible to delineate between locally commissioned services (via Clinical Commissioning Groups) and specialised commissioned services (via NHS England). We are working on this.

2. DEROGATION OF SERVICES

The attention with which hospitals have applied the criteria set out in the specification has varied and some surprises have emerged during this process. The CRG intends to tighten the specifications to avoid misinterpretation.

3. DRUGS

Central policies are being developed for such drugs as pegvisomant, cinacalcet, tolvaptan, pasireotide etc. Inevitably there is a backlog; the current estimate is 6 months. The aim is to avoid regional, so-called postcode, prescribing. However, for the moment individual funding requests need to be made, and we appreciate that, although temporary, this is laborious. The second issue is who pays for drugs. Those used in specialised endocrinology should clearly be paid for by NHS England, and we are working towards this.

I have organised a meeting at the Royal College of Physicians of the CRG Chairs on 14–15 July, so that we can hopefully solve these problems.

Along with the CRG's Deputy Chair, Neil Gittoes, and Commissioner, Ursula Peuple, I am happy to answer your questions aimed at understanding the issues and improving the system.



JOHN WASS
Chair, Specialised Endocrinology CRG, and External Clinical Relations Advisor, Society for Endocrinology

If you have any questions or comments, please contact us via endocrinologist@endocrinology.org. You can read more at <http://bit.ly/RGgbTa>

FROM THE CHIEF EXECUTIVE'S DESK: NO POOR RELATIONS



WRITTEN BY LEON HEWARD-MILLS

Relationships are important. From our research and audit projects, through our public engagement work, to the work of our journal Editorial Boards, the success of all Society activities is dependent on strong partnerships.

For us to meet our aim of promoting and supporting endocrinology worldwide, working with other organisations is essential. We have recently collaborated with a number of international endocrine societies to organise international events. As Laura Udakis mentions on pages 22–23, the International Clinical Update in Endocrinology (ICUE) was held in Hyderabad in February, in collaboration with the International Society of Endocrinology, the Endocrine Society (USA) and the Endocrine Society of India, and in October 2014 members will be participating in the Annual Academic Sessions of the Endocrine Society of Sri Lanka. These links will serve us well as we look to develop our global presence.

Some of the Society's most important relationships are those between our members, which are the life force of our community. The fruits of these relationships are evident closer to home at the Society's annual BES conference (see pages 18–19). In Liverpool this year I was thrilled to see contributions from world-leading endocrine scientists and clinicians and the valued interactions between members of every level – this willingness of the most senior to share knowledge and mentor entry level members is a particular and excellent attribute of our Society. Don't forget that the Society's BES conference is moving to the autumn from 2015. I look forward to meeting again in Edinburgh next November.

Endocrine Networks are another manifestation of productive relationships between members. It's exciting to see the sheer enthusiasm of our members championing their particular areas of expertise, creating communities that support the work of endocrinologists working in those areas, as well as raising their profile. Appropriately enough for this issue, our first Endocrine Network has been founded, in reproductive endocrinology and biology, and is led by Stephen Franks and Andrew Childs (page 25). The networks are open to all members – participation is actively encouraged. Full details of the Society's Endocrine Network programme are available on our website at www.endocrinology.org/endocrinenetworks. I will enjoy seeing the outputs of the new groups over the next few months.

Of course the strongest relationships are ones that evolve over time and that incorporate new ways of thinking and fresh approaches. This is already apparent through the Presidency of Steve O'Rahilly, who is interviewed by Tony Coll on pages 20–21. I am looking forward to seeing how Steve's leadership will help the Society develop over the coming years.

LEON HEWARD-MILLS
Chief Executive, Society for Endocrinology
and Managing Director, Bioscientifica Ltd
Email: leon.heward-mills@endocrinology.org

CLINICAL UPDATE

SAVE THE DATE

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KEY DATES

Case submission deadline

8 September

Early bird deadline

1 October

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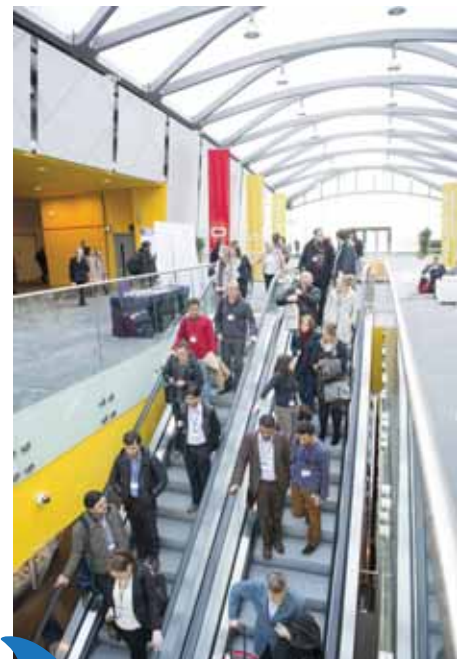
Scientists, clinicians, nurses, sponsors, patient groups, exhibitors and speakers came together to experience cutting-edge endocrine research and clinical practice, complemented by skills workshops, networking sessions and social events. This is what our delegates said...

“Having the cutting-edge scientific programme as well as opportunities for people to brush up on their practical skills makes this conference unique”



‘REALLY WELL RUN, THE QUALITY OF SCIENCE IS HIGH - I THINK IT’S TERRIFIC’

“Great networking, great sessions, great science”



‘It’s a great opportunity to present your science and get some really crucial feedback, to meet and mix with eminent people within the field and to really take the opportunity to speak to as many people as you can’



'I'm a medical student who is very interested in endocrinology. I was really grateful for the free place and I'm making the most of it. It's a great place to come to get inspired and it's certainly done that - I can feel the passion in the air!'



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YOUR NEW PRESIDENT: STEPHEN O'RAHILLY

WRITTEN BY TONY COLL



This spring at the Society for Endocrinology BES conference, Professor Sir Stephen O'Rahilly formally became President of our Society. For those of you who have never had the pleasure of meeting Steve, *The Endocrinologist* thought it only proper that we introduce him to you all. I caught up with him at the Wellcome Trust-MRC Institute of Metabolic Science to talk about his formative years, and to ask him about the challenges facing endocrinology.

The walls of Steve O'Rahilly's office are discreetly decorated with just some of the many honours he has garnered, and I could fill this page by listing his current job titles alone. Yet such a dry list would be a disservice to a man who, I think, has never rested on his laurels, but has an infectious, child-like energy and enthusiasm for finding out stuff – and can't quite believe that someone pays for him to do a job that, for the most part, doesn't feel like work at all.

EARLY INSPIRATION

Born into a blue collar suburb in north Dublin, he and his cousins were the first generation of their families to have a university education. Steve was a voracious reader from an early age, tackling anything he could get his hands on. Works such as *The Lives of a Cell* by the medical polymath Lewis Thomas and an article on prolactin in an issue of *Scientific American*, bought by his pharmacist father, are fondly remembered as inspirational pieces in their descriptions of how molecular machinery can explain the occurrence of much larger scale processes.

Medicine seemed a logical choice to combine the desire 'to do something worthwhile' with science, and he trained at University College Dublin. A craft speciality was never on the cards ('ten thumbs'), and he felt much more at home with narrative, thinking specialities. He came to England with the view that this would further his training before he returned home to work as an endocrinologist in Ireland.

After spells at Barts and the Hammersmith in London, he thought it would be good to do a bit of research. He visited Robert Turner in Oxford, telling him that he wasn't that interested in diabetes but really wanted to do endocrinology because he loved hormones. Turner's riposte, 'Well ... what do you think insulin is then?' was a less than auspicious start!

Despite this, Turner gave him a chance, the gamble paid off, and Steve thrived. He still views Turner as one of his all-time heroes, considering him an inspirational thinker, a 'do-er' and someone who brought endocrine sensibilities to the study of diabetes at a time when many thought 'never the twain shall meet'.

TAKING TECHNOLOGY TO THE CLINIC

While in Oxford, Steve was caught up in the groundswell of excitement of the molecular biology revolution, and undertook some of the first linkage studies in type 2 diabetes. A spell at Harvard was also hugely influential, not least because it confirmed that his forte lay not in the meticulous craft of bench science (attempts to clone the glucagon-like peptide-1 receptor were not hugely successful) but in the linking of new technologies to clinical problems.

He returned to the UK in 1991, planning to use skills learnt in Boston to start up a small lab in Cambridge and tackle the basis of the insulin resistance in a group of patients that Nick Hales had collected. Reflecting honestly on the world view of obesity at the time, O'Rahilly recounts that he, like many of his colleagues, thought it was pretty much 'a cosmetic side effect of poor health choices'.

However, his thoughtful endocrine perspective came to the fore when Steve saw a patient with severe obesity and nocturnal hypoglycaemia. Biochemical analyses determined that, in addition to an abnormality of proinsulin processing, there was evidence of impaired processing of pro-opiomelanocortin and hypogonadotropic hypogonadism, all in keeping with a more generalised defect in processing prohormones. In time, the patient was indeed shown to have a mutation in the gene encoding prohormone convertase 1 (PC1), but this case provoked some hard thinking about the biology of obesity and strongly suggested that previous dismissive dogmas were ripe for revision.

The 'big bang' moment came with the discovery of leptin in 1994. The appearance of the Friedman paper,¹ describing how a peptide from adipose tissue might function in a signalling pathway to regulate the size of the body fat depot, was a total game changer. The report from Steve's lab in 1997 of the first case of congenital leptin deficiency in two first cousins with severe obesity² also proved to be a landmark, signalling the beginning of a productive period which transformed the landscape of obesity and metabolism. Having greatly shaped our knowledge of human leptin-melanocortin biology, the O'Rahilly lab continues to define and characterise previously unrecognised conditions in obesity, insulin resistance and lipodystrophy.

'If not medicine, what would he have done? After a glorious spell playing for Manchester United, a successful career as a singer songwriter in the style of Tom Waits, and then as a Nobel Laureate, he would like to write "the great Irish novel".'

ENDOCRINE CHALLENGES TO COME

So, how much more is there to find out, particularly in the current genomic era? Will the ability to spit in a tube, pop it in the post and await a personalised analysis of your DNA for less than \$100 change how things are done in the future?

O'Rahilly admits that it was both a little disappointing and a little scary to find that we only have around 20,000 genes, but still sees great challenges ahead. For example, the roles of all those non-coding, regulatory and intronic regions remain pretty much on the dark side of the biological moon. There are also tough questions about how to handle all the data that are being generated by mega-scale genomics and then curate it in a way that is meaningful to the humans whence it came.

What about the future of clinical endocrinology? With current hospital practice and junior doctors banished to the wards to meet ever-increasing inpatient demands, O'Rahilly admits there is a danger that all the wonderful stuff we do in clinic as ambulatory care is hidden away, invisible to the very people we need to inspire. When it comes to basic science, O'Rahilly is certain we still need to attract the brightest and the best. However, with disciplines like neuroscience, cancer and immunology appearing to be far 'cooler', there is a danger that our specialty could feel the squeeze, particularly when it comes to more traditional biochemical endocrinology.

Through his work with the Academy of Medical Sciences, he has seen how it is possible to both promote excellence and nurture the next generation of medical researchers, and he feels that maintaining a high standard of basic and clinical science is a central tenet of his Presidency.

A TALE YET TO TELL

As I write this up (relieved that I didn't have to revert to my *Smash Hits* interview questions that I'd written down in advance), I'm recalling something Steve once said to a journalist who asked, 'If not medicine, what would you have done?'. Without hesitation, Steve replied that, after a glorious spell playing for Manchester United, a successful career as a singer songwriter in the style of Tom Waits, and then as a Nobel Laureate, he would like to write 'the great Irish novel'.

Now the old adage goes that everyone has one novel inside them ... and for the majority that's where it should stay. Yet I reckon O'Rahilly's text would be worth a read. I think we should be very pleased that our new President has a command of language that means, as well as generating great ideas and prosecuting worthwhile, intelligent science, he is a master of telling the story in a way that cannot fail to engage the widest possible audience, support up and coming colleagues and advance scientific excellence along the way.

TONY COLL

Associate Editor, The Endocrinologist

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EXCEL IN YOUR RESEARCH

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'Best course I have ever been on - life changing - will definitely be back next year for Track 2'

'Fantastic opportunity to meet colleagues and learn from experts, it answered many questions an early career scientist maybe asking'

'A highly enjoyable experience, necessary for anyone considering academic career progression'

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REACHING OUT - TO IMPROVE PUBLIC HEALTH

WRITTEN BY LAURA UDAKIS



Working with others is a priority for our Society. Collaboration with external partners will enable us to strengthen and expand the reach of our work towards improving public health. As well as our Corporate Supporters, who continue to help us complete this mission, the Society collaborates with many organisations on projects spanning all aspects of our work.



ENGAGE | SUPPORT | ADVANCE

SUPPORTING YOUR CAREERS



Over the last year, our Young Endocrinologists' Steering Group has strengthened links with the Young Diabetologists & Endocrinologists' Forum (YDEF), with the aim of jointly organising education events for clinical specialists in endocrinology and diabetes.

'Collaborations are essential in the training and development of scientists- and clinicians-in-training. I am delighted that the Young Endocrinologists' Steering Group has strengthened its links with the YDEF, sharing the same aim and passion to organise education events, not only for clinical specialists, but also basic scientists in endocrinology and metabolism.'

Samantha Mirczuk,
Chair, Young Endocrinologists' Steering Group



ADVANCING ENDOCRINOLOGY

The Society works with Ipsen and the Clinical Endocrinology Trust to continue the long-running UK Acromegaly Register. By July 2013, over 3,000 patients were on the Register. This year we have strengthened our collaborations with research staff and encouraged centres to undertake database training to allow continuous updating. Next year, generation of regular reports will provide project updates to those involved.



'The VoYS workshop provided some fascinating insights into the interface between science and the media. I left enthused to take the first steps in communicating to a wider audience.'

Zaki Hassan-Smith,
Young Endocrinologist

COMMUNICATING YOUR WORK

In the past year, more of you than ever have taken part in Voice of Young Science (VoYS) media workshops run by Sense About Science. These workshops provide invaluable training for the Society's early career members, introducing them to how the media work and giving practical tips from journalists and advice from media-experienced scientists.



During National Science and Engineering Week, the Society's Young Endocrinologists beat fierce competition to present posters of their work at 'SET for Britain' in the House of Commons (see article opposite). This event aimed to support the work of early career researchers and recognise them as a vital asset and investment for the UK.

IMPROVING PATIENT CARE

One of your Society's long-term objectives is to facilitate communication between the medical community and endocrine patient support groups. We currently help promote the work of over 20 patient support groups. You can read about the work of one of these, the Turner Syndrome Support Society, on page 30.

'The ADShG's trustees are grateful to the Society for Endocrinology for its role in co-ordinating contacts across all the patient support groups affiliated to the Society, and for its support in our awareness-raising work. Staff at the Society have been quietly supportive in featuring our work in various publications, and in facilitating our participation at Society events. Over recent years, the Society has increasingly opened its doors to us.'

Katherine White, Chair, Addison's Disease Self Help Group

RAISING THE VOICE OF ENDOCRINOLOGY

We worked with a number of learned societies to organise Voice of the Future 2014 at the Houses of Parliament (see page 25). At this year's event, held during National Science and Engineering Week, the Society's Young Endocrinologists put forward two questions to science policymakers on the future of UK science and the role of endocrinologists.



You, our members, also inform our policy development alongside organisations such as the Society of Biology. One example is the Concordat on Openness about Animal Research, which aims to set out how organisations will be more open about the ways in which animals are used in scientific, medical and veterinary research in the UK.



'@Soc_Endo @Society_Biology Thank you very much for today #VOF2014 I am so grateful for the experience and wish the best for British science!'
Theresa Mina, Attendee, via Twitter



ENGAGING WIDER AUDIENCES

Your Society works in partnership with several national science festivals to engage the public in discussion over topical areas of endocrinology. This year we've organised debates around the role of hormones in attraction and relationships, as well as the late effects of cancer therapy.

GOING GLOBAL

Successful collaboration with the Endocrine Society of India (ESI), International Society of Endocrinology (ISE) and the Endocrine Society (USA) led to the International Clinical Update programme in Endocrinology (ICUE) in India. This event, held in February 2014, brought together 1,000 trainees, endocrinologists and general physicians practising in India and neighbouring regions. The Society is also building links with the Endocrine Society of Sri Lanka by supporting our UK clinical members to present their work at the Annual Academic Sessions of the Endocrine Society of Sri Lanka in October 2014.

LAURA UDAKIS
Marketing & Communications Manager,
Society for Endocrinology

SET FOR BRITAIN 2014

This year, the Society took part in SET for Britain, a scheme that allows early career researchers to present their work to members of both Houses of Parliament at Westminster. Here, one of the Society's attendees, Opeolu Ojo, describes his day at the House of Commons.



Opeolu Ojo presents his poster at SET for Britain

When I first read the email about SET for Britain from the Society of Endocrinology, I confess that my first thought was, 'Will this be worth the effort?' However, after some consideration and reading more detailed information, I was convinced that it was an event I shouldn't miss.

My desire to attend was boosted when my abstract was selected out of over 400 applications in biological and biomedical sciences, and a travel grant from the Society for Endocrinology provided the final impetus I needed to attend.

It was an invaluable experience to stand among my peers, senior scientists, executives of learned societies and legislators to present a summary of my ongoing studies on a recently identified amphibian skin peptide for the treatment of type 2 diabetes. Questions from curious participants who were not familiar with my research, combined with insightful scientific comments from experts in the field, provided me with hugely encouraging feedback on my studies, and renewed my passion for research in endocrinology.

Interactions with other early career scientists and strategic alliances formed with some senior colleagues at the meeting are already producing positive results, particularly in terms of further research training opportunities in key techniques that are critical to my studies. I will be visiting the University of Plymouth later in the year to learn the patch clamp technique.

As well as the travel grant provided by the Society for Endocrinology, I was extremely pleased to meet Society staff at the event, including CEO Leon Heward-Mills, Business Development Manager Maja Lubczanska and Professional Affairs Officer Kate Bowman. Their presence showed me that the Society has a genuine interest in helping young scientists develop their careers.

OPEOLU O JO
Postdoctoral Researcher, University of Ulster

You can find more information on SET for Britain at www.setforbritain.org.uk.

OPENING DOORS TO A BRIGHT FUTURE: SOCIETY FOR ENDOCRINOLOGY EARLY CAREER GRANTS



WRITTEN BY TIJANA MITIĆ

In August 2012, Tijana was awarded a Society for Endocrinology Early Career Grant to investigate the influence of diabetes on vascular cells during muscle ischaemia. Here, she discusses the impact the grant had on her career.

More experienced scientists say that the hardest thing to achieve during your early academic research is independence from your principal investigator. 'Budding off' and finding your own work niche is not easy. One of the greatest barriers is finding a sponsor in a different department or university, in order to apply for an independent fellowship following a postdoc position. That said, working towards any grant application requires completion of some pilot experiments.

'As a result of this funding, I have learnt to prepare DNA libraries for sequencing using ChIP-DNA samples'

In my last postdoc role, I had the challenging task of setting up new ideas in a non-epigenetics lab that had a strong background in vascular surgery and post-ischaemic angiogenesis. The process of vascular recovery inspired me most because, as with cancer cells, vascular cells undergo various epigenetic alterations before reaching their repaired/healthy state again. Moreover, post-ischaemic vascular angiogenesis and consequent blood flow recovery are compromised by diabetes.

'As a lab, we were able to attract new collaborations and strengthen previous ones'

My postdoc project investigated how diabetes influences vascular cells during muscular ischaemia in a diabetic mouse model. Research suggests that high glucose and low oxygen levels can independently induce modification of histone proteins in human endothelial cells lining the blood vessels. These modifications, known as epigenetic changes, are rather dynamic in response to high glucose, but have not previously been investigated in association with ischaemia. I consequently set out to investigate the impact of histone modification driven by EZH2 protein, and I explored whether this enzyme can repress genes necessary for blood vessel development under diabetes and ischaemia.

I developed my skills in epigenetics as a result of experience gained through an Albert Renold Fellowship from the European Federation for Study of Diabetes (EFSD) when I visited a cancer lab at the European Institute of Oncology (IFOM-IEO) in Milan, Italy. It was this experience that laid the foundation for my application for a Society for Endocrinology Early Career Grant. This grant allowed me to dramatically expand the understanding of the epigenetic regulation of endothelial cells by diabetes. As a result of this funding, I have learnt to prepare DNA libraries for sequencing using ChIP-DNA samples (ChIP-seq library preparation). Subsequently, my project has expanded to determine mechanisms for repression of endothelial nitric oxide synthase (and other angiogenic genes) in endothelial cells due to EZH2 upregulation in diabetes and muscular ischaemia. Additionally, it helped to identify novel therapeutic targets for future research, like microRNA-101 in endothelial cells in diabetes. As a lab, we were able to attract new collaborations and strengthen previous ones, such as that with Professor Craig McArdle (Bristol) for the use of IN Cell Analyzer techniques to use fluorescence to scan and visualise histone changes in endothelial cells.

'Results have led to work for other postdocs in the lab, while also being presented as manuscripts for publication'

The Early Career Grant covered the direct cost of my research project for a year and my studies have further complemented a number of projects being conducted within the laboratory of Professor Emanuelli. Results of the above projects have led to work for other postdocs in the lab, while also being presented as manuscripts for publication. The positive findings from the work funded by the grant have reinforced my hypothesis and contributed to a bigger grant application. In November 2013, we were successful in obtaining a significant project grant from the EFSD (£90,100) under the sponsorship of Professor Emanuelli, further raising the profile of the early vascular-epigenetics lab.

'The findings from the work funded by the grant have reinforced my hypothesis and contributed to a bigger grant application'

Thus the grant from the Society for Endocrinology has not only provided me with research independence within the mainstream focusing on epigenetic memory, but also given me research autonomy within the lab, and the challenge of addressing my research hypothesis. Sometimes the opportunities you receive enable you to reflect upon how you might have seen academic research, science funding and your academic career in the first place. Certainly, a positive attitude, belief and enthusiasm are crucial components in adding a spark to any grant or fellowship application.

TIJANA MITIĆ

Postdoctoral Scientist, University of Bristol

After completing her PhD, early career scientist Tijana Mitic conducted postdoctoral research into molecular and vascular biology under Professor Jonathan Seckl at the University of Edinburgh. She then joined Professor Costanza Emanuelli's laboratory at the Bristol Heart Institute where she has now completed a postdoctoral role and is applying for an independent research fellowship. Her main interest is the epigenetic regulation of endothelial genes by non-coding RNA in pathophysiology.

APPLY FOR AN EARLY CAREER GRANT

Do you have a research idea but don't know where to apply for funding? Why not consider applying for up to £10,000 through our Early Career Grant scheme? The next application deadline is 27 November 2014. More information can be found at www.endocrinology.org/grants/grant_earlycareer.html.

VOICE OF THE FUTURE 2014

Voice of the Future invites early career researchers to attend Parliament to question a selection of MPs and advisors about their views on key issues faced by scientists and researchers today. Society member Rebecca Perrett recounts the experience and what she learnt.



Society members Lucy Brooks, Rebecca Perrett, Theresia Mina and Zaki Hassan-Smith at Voice of the Future 2014

On 19 March, I was joined by three other members of the Society for Endocrinology at Voice of the Future 2014, a Society of Biology event hosted by the Select Committee on Science and Technology. The Science and Technology Select Committee exists to ensure that Government policy and decision-making are based on good scientific and engineering advice and evidence.

During this event, representatives of learned and professional societies and other interested parties sat at the committee table and questioned MPs on science policy. These included members of the Select Committee; the Minister for Universities and Science, David Willetts MP (Conservative); the Shadow Minister for Higher Education, Liam Byrne MP (Labour); and the Government's Chief Scientific Adviser, Sir Mark Walport. The event was introduced by the Speaker of the House of Commons, John Bercov.

Society member Zaki Hassan-Smith (Birmingham) questioned how a Labour government would fund research in endocrinology. Liam Byrne replied that they would conduct a complete review of spending, and are keen to grow pharmaceuticals and improve life science relationships with the NHS, as well as links to Asia. Theresia Mina (Edinburgh) asked how the Government is encouraging employers to value STEM (science, technology, engineering and mathematics) research skills. David Willetts responded that the Government has brought together industry and the BBSRC and/or MRC to jointly fund PhD programmes.

All Society for Endocrinology representatives felt that this was a great opportunity to understand the workings of the Select Committee and the various considerations Government must face when deciding science policy. As scientists, we can get involved, for example by submitting evidence to a Select Committee inquiry, taking part in the Royal Society's MP-scientist pairing scheme, or by simply writing to our local MP explaining our research. Whilst we all enjoyed being a politician for a day, I think we'll remain scientists ... for now!

REBECCA PERRETT

Postdoctoral Researcher, University of Bristol

You can watch the session in full at
www.bbc.co.uk/democracylive/house-of-commons-26632445.

NEW SOCIETY ENDOCRINE NETWORK IN REPRODUCTIVE ENDOCRINOLOGY AND BIOLOGY

Reproductive endocrinology is a subject that tends to fall between specialties. In clinical practice, and even in clinical research, it is often found within the remit of reproductive medicine, as a subspecialty of obstetrics and gynaecology. Basic research in reproductive endocrinology is more likely to be presented at meetings of the Society for Reproduction and Fertility (SRF) or Society for the Study of Reproduction than at the Society for Endocrinology BES conference.

The establishment of the new Society for Endocrinology Endocrine Networks to replace the SIGs (Special Interest Groups) has provided a perfect opportunity to set up a broad-based Endocrine Network in Reproductive Endocrinology and Biology (ENREB) as a platform for scientific meetings, collaborative research and teaching, which will appeal to basic and clinical scientists in the field, as well as clinical endocrinologists.

ENREB'S AIMS INCLUDE:

- to provide input to the Programme Committee regarding plenary lectures, symposia and communication sessions at the Society for Endocrinology BES conference
- to collaborate more closely with other relevant scientific societies, including the SRF
- to encourage collaborative research in reproductive endocrinology
- to provide a forum for teaching and training in reproductive endocrinology, and
- to promote public engagement in endocrinology through links with patient support groups (and the media) and by engaging in public science forums such as science festivals.

Proposals for the coming months include a satellite symposium on ovarian endocrinology at the World Congress of Reproductive Biology in Edinburgh in September 2014 and an European Society of Endocrinology/Society for Endocrinology basic science conference aimed at young endocrinologists in the field.

ENREB will be co-ordinated by myself and by Andy Childs (London), and our first step is to gather an enthusiastic and representative committee to help plan and run the network's activities. We are looking forward to it enormously and we are very grateful to the Society for Endocrinology for approving and supporting the establishment of our new network.

STEPHEN FRANKS

Network Lead, ENREB, and Professor of Endocrinology, Imperial College London

For more information on the Society's Endocrine Networks or to propose a new Endocrine Network yourself, visit www.endocrinology.org/endocrinenetworks.

**LISA SHEPHERD
NURSE
COMMITTEE
CHAIR**



This year's Society for Endocrinology BES conference in Liverpool yielded the largest number of submission of posters by nurses, which is hugely encouraging. Presenting this work provides a valuable opportunity for you to share your work with the endocrine community, especially fellow nurses.

It is also a chance for you to see how your nursing colleagues work in other centres, to learn about services they have developed, to look at evaluation of their services and to understand how these initiatives impact on patient care.

I would like to congratulate the two nurse poster prize winners from the Society BES conference, Rhianna Mason (Exeter) and Jean Munday (Portsmouth) on their work. Congratulations also due to Diana Mantripp (Oxford) for achieving her Certificate in Adult Endocrine Nursing.

Networking, education and sharing best practice are high on the nursing agenda not only nationally but internationally. We look forward to presenting at the nurse session during the joint meeting of the International Society of Endocrinology and the Endocrine Society (ICE/ ENDO 2014) at Chicago, IL, USA in June, and the continued development of international nurse collaboration.

I also hope to see you at the Endocrine Nurse Update in Birmingham on 15-16 September. This is an annual 2-day residential course for established and new-to-post endocrine nurses. There is a rolling programme of topics which repeats every 3 years. See www.endocrinology.org/meetings/endocrinurse for details.

LISA SHEPHERD

CONGRATULATIONS

Many congratulations to Diana Mantripp (Oxford) who was awarded her Society for Endocrinology Certificate in Adult Endocrine Nursing at the recent Society BES conference. This Society-run scheme recognises nurses who promote good practice in patient care and clinical management and have worked on their development as endocrine nurses. Further details can be found at www.endocrinology.org/endocrinurse.

**NURSES AT SOCIETY
BES CONFERENCE**



Jean Munday receives the Annette Louise Seal Memorial Award from retiring Society President Ashley Grossman

The Society for Endocrinology BES conference again enjoyed a busy nurses' programme. Wednesday morning saw a clinical session on the long term management of patients with Cushing's syndrome. In the afternoon, fascinating talks examined endocrine nursing research, including independent nursing studies, nursing in the context of a clinical trial, and how to carry out a clinical audit.

Congratulations are due to Jean Munday (Portsmouth) who won the Annette Louise Seal Memorial Award for her poster 'Steroid group education: developing a curriculum ensures good nursing practice is maintained'. This prize is awarded by the Addison's Disease Self Help Group to the nursing abstract which best advances the clinical management of adrenal insufficiency.

We also congratulate Rhianna Mason (Exeter) who received the Clinical Endocrinology Trust Prize for the best abstract in the 'Nursing Practice' category. Her abstract was entitled 'Introduction of a protocol and endocrine specialist nurse ward visits in the management of hyponatraemia'.

All abstracts from the conference can be viewed at www.endocrine-abstracts.org.



**ENDOCRINE
NURSE UPDATE**

15 - 16 SEPTEMBER 2014
Aston University, Birmingham

The UK's premier course for endocrine nurses, providing best practice updates and the latest in treatment developments

www.endocrinology.org/meetings/endocrinurse

"A fantastic update and opportunity to meet lots of other nurses working in the area."

(Endocrine Nurse Update 2013 attendee)

OBESITY UPDATE



The very first Obesity Update meeting, aimed at the developing field of bariatric medicine, was held at the Royal College of Physicians, London, on 13 January.

Supported by the Society for Endocrinology, the meeting was a joint effort between APSO-UK (the Association of Physicians Specialising in Obesity UK) and ASBP (the American Society of Bariatric Physicians). It was the first opportunity to bring together obesity physicians and allied healthcare professionals to discuss the challenges and complexities of obesity.

Obesity Update opened with a provocative talk by Julian Barth (Leeds), setting the scene regarding the challenges of complex obesity. This was followed by insights into the colourful life of adipocytes (Fredrik Karpe, Oxford), the role of physical activity in obesity (Debbie Horn, Houston, TX, USA), and the increasing number of emerging pharmacotherapies (John Wilding, Liverpool). There were lively discussions on the role of bariatric physicians by Nick Finan (London) and Richard Lindquist (Seattle, WA, USA). This was followed by a joint presentation on transatlantic views on bariatric services by Shahrhad Taheri (London) and David Bryman (Scottsdale, AZ, USA).

Both the audience and the participants enjoyed the excellent case discussions and debates supported by expert panels and chairs. The cases included genetic and psychiatric disorders of complex obesity, complications of bariatric surgery including hypoglycaemia and nutritional deficiencies, and other hot topics in bariatric surgery. We congratulate the winners of the top three case presentations.

Steve Bloom (London) ended the day with a superb keynote lecture on appetite and gut hormones, leaving us all hungry for more! The general feedback was very positive and the conference well received. We thank all speakers, sponsors, panels and chairs, and especially ASBP, for a successful day. We very much hope to make the Obesity Update an annual event and look forward to seeing you all in January 2015.

BARBARA MCGOWAN

Consultant Endocrinologist, Guy's and St Thomas' Hospital, London

SHAHRHAD TAHERI

Visiting Professor of Medicine, King's College London

Obesity Update 2014 was supported by a Society for Endocrinology Sponsored Seminar Grant. Further details of this grant scheme are available at www.endocrinology.org/grants/grant_sponsoredseminars.html.

BRITISH THYROID FOUNDATION AWARDS 2014

THE BRITISH THYROID FOUNDATION (BTF) INVITES APPLICATIONS FOR THEIR ANNUAL AWARDS



The BTF Research Award 2014 is available for research that is specifically directed to the study of disorders such as hypothyroidism, hyperthyroidism, thyroid cancer, thyroid eye disease and children's thyroid disorders, or investigations into the basic understanding of thyroid function. The award is for £20,000 and the deadline for applications is 31 August 2014.

The Evelyn Ashley Smith Award for nurses is intended to improve care for patients with thyroid disorders. The BTF is offering two awards for nurses, endocrine nurses, midwives and healthcare professionals with an interest in thyroid disorders. One award of up to £500 is to help cover conference/training expenses, including registration fees and/or travel costs. The second award of up to £1,000 will help support a specific project lasting 1 year, or else support an on-going project or reward a piece of work already completed, but not yet published. The closing date for receipt of applications is 1 July 2014.

Please see www.btf-thyroid.org for more details of the awards and application forms.

TEDCT NURSE/HEALTH PROFESSIONAL BURSARY

TED_{ct}

The Thyroid Eye Disease Charitable Trust (TEDct) Nurse/Health Professional Bursary can be used to support education (e.g. to pay for course fees), to meet travel/accommodation expenses to attend such courses, or to cover a combination of these.

Applications should generally be for sums up to £500, though requests for larger amounts may also be considered. The bursary must be used only as stated on the application form and the course should be related to your work with patients with TED or be of benefit to your working practice with such patients. Further eligibility criteria and conditions of use will apply – these are available with the application forms.

Successful applicants will be required to present a session at a TEDct Patient Information Meeting and write an article for the *TEDct Newsletter*. Both must be understandable to a lay person.

Please contact TEDct for further details/application forms and eligibility criteria (TEDct, PO Box 1928, Bristol BS37 0AX, UK; Tel: 0844 800 8133; Email: ted@tedct.co.uk).

RICHARD MICHAEL (1924–2014)

WRITTEN BY TONY PLANT



Richard Michael was born in London in 1924 and died peacefully in his sleep in Atlanta on 5 January 2014. He was educated in England and graduated from University College Hospital Medical School, London, in 1951. A few years later, as a senior resident at the Maudsley Hospital, Richard fell under the spell of Geoffrey Harris, Professor at the Institute of Psychiatry, University of London. Harris, who was pursuing the notion that steroids influence particular neurones in the brain, became Richard's PhD supervisor.

For his thesis, Richard examined the neural mechanisms underlying the action of oestrogen to induce oestrous behaviour in the domestic cat. This was indeed a wise choice because the cat provides a particularly good experimental model, as the display of oestrus is dramatic, stereotypic and absolutely dependent on stimulation by the ovarian hormone. Richard received his PhD in 1960.

'Richard provided compelling evidence that the brain was where oestrogen acted to induce behavioural oestrus'

With Harris and Patricia Scott, Richard later provided compelling evidence that the brain was where oestrogen acted to induce behavioural oestrus, as hypothalamic implants of the hormone could elicit the behaviour without a concomitant systemic effect on the reproductive tract. He used autoradiography to provide the first evidence that certain neurones in the hypothalamus possess a 'special capacity for accumulating and retaining hormone', a finding published in *Science* in 1962, several years before the concept of an oestrogen receptor formally emerged.

As the sixties progressed, Richard turned his attentions to the rhesus monkey, a representative highly evolved primate with a true menstrual cycle similar to the human female. It proved a much more challenging model than the cat, and Richard and his colleagues spent more than a decade (1) defining the male and female components of sexual behaviour, (2) modifying stereotaxic approaches to interrogate hormone sensitive regions of the primate brain, (3) developing operant indices of motivation, and (4) adapting radioimmunoassay procedures to accurately quantify low circulating concentrations of ovarian steroids throughout the menstrual cycle and correlate them with objective behavioural parameters. This work culminated after Richard had emigrated to the USA in 1972, when he accepted a joint appointment in the Departments of Psychiatry and Anatomy at Emory University School of Medicine, and founded the Biological Psychiatry Research Laboratories at the Georgia Mental Health Institute.

Throughout his career, Richard wore two hats: academic psychiatrist and basic scientist exploring fundamental mechanisms underlying the neuroendocrine basis of sexual behaviour. His work as an investigator was creative, meticulous, exhaustively analysed, unambiguously illustrated and relayed to others in a robust and linear fashion with a remarkably efficient use of words. Richard was an outstanding lecturer. As a mentor, he was demanding of his students but also a constant source of inspiration. In addition to his scientific contributions, which were of the highest calibre, widely recognised and greatly respected by his peers, Richard will also be remembered for his larger than life character and exceptional wit. Richard officially retired in 1994 but he remained active in the field for several years after that. He is survived by his wife, Anne, their four children, Simon, Adrian, Caroline and Crispin, and nine grandchildren.

TONY PLANT

FURTHER READING

Michael RP & Zumpe D 2005 *Neuroendocrine Aspects of Primate Sexual Behavior*. Loganville, GA, USA: REAL U.

**SOCIETY FOR
ENDOCRINOLOGY
CORPORATE
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or contact amanda.helm@endocrinology.org.

JAMES F TAIT FRS (1925–2014)

WRITTEN BY JOHN COGLAN & GAVIN VINSON



©GODFREY ARGENT STUDIO

James F Tait and his collaborator, Sylvia Simpson, later his wife, for some years in the 1950s held the attention of the world of biomedical science. Tait was only in his 20s at that time, a lecturer in physics at the Middlesex Hospital Medical School in London. Sylvia worked in the School's Courtauld Institute of Biochemistry.

Their story starts with the discovery and characterisation of the range of steroid hormones. This had begun before the Second World War, but was given extra impetus in the USA during the war, after rumours that German pilots were using them to enhance their performance. Edward Kendall's team at the Mayo Clinic in Minnesota had, by the late 1940s, isolated about 30 different compounds from bovine and porcine adrenal glands, and Tadeusz Reichstein's team in Basel had achieved similar success. The huge clinical value of these discoveries was demonstrated, notably the anti-inflammatory actions of the best known, cortisone. The main secretory product of the cortex of the adrenal gland is, however, cortisol, and this is still widely used under its pharmacological name, hydrocortisone.

The scientific world was divided over whether there was more to uncover. There was an annoying residue of the various extracts that seemed to contain something with a quite different activity, concerned with sodium and potassium balance: this was called mineralocorticoid activity. The active substance resisted crystallisation, and thus could not be purified. Yet this material, vanishingly low in amount, turned out to be essential for life.

Against the giants of the world of medical science, it seemed unlikely that a pair of young scientists working on their own in London at that time could achieve success where the major groups had not. But the Tait's had two technical advantages. One was the recent development of paper chromatography to separate steroids. The second was the insight that James Tait brought to bear on the assay of mineralocorticoid activity. Radioactively-labelled products were recently available from the Radiochemical Centre in Amersham, and it was the use of the ratio of radioactive sodium and potassium excreted into the urine of rats that the Tait's used to detect mineralocorticoid activity with exquisite sensitivity. As a result, they purified and characterised the biological activity and, in part, the chemical structure of a compound they called electrocortin.

Collaboration with Reichstein led to its complete chemical characterisation, and a change of name to aldosterone. This was Nobel Prize-winning science, but, perhaps because of Reichstein's earlier award and the large group eventually involved, the prize eluded the Tait's. They were however elected Fellows of the Royal Society in 1959; husband and wife elections to the Royal Society are, needless to say, extremely rare.

Today, there is a resurgence of interest in aldosterone with the finding of its role in the development of fibrotic changes in cardiovascular disease, and it may be involved in up to 20% of patients with hypertension.

In 1958, the Tait's joined the 'brain drain' to the better-resourced USA. It was Gregory Pincus, director of the Worcester Foundation for Experimental Biology in Shrewsbury, Massachusetts, who head-hunted them to set up a new division. Pincus was working on the oral contraceptive, so research into another area of steroid endocrinology was a logical development for both the Foundation and the Tait's.

At the Worcester Foundation, James made his second remarkable contribution to hormone science. At that time, in the 1960s, assays of the steroid hormones in circulating blood were extremely laborious and difficult. Exploiting again his training in physics, following infusions of radioactively-labelled hormones into humans, he developed mathematical treatments to calculate hormone secretion rates and clearance from changes in the ratio of labelled to unlabelled hormone in urine or blood. This developed into a new field of study, hormone dynamics, providing data then unattainable otherwise. It also introduced

the concept of the 'prehormone' – a secreted substance only converted to the active hormone at its site of action (e.g. the adrenal secretion of the prehormone androstenedione in women is the primary origin of (peripherally formed) testosterone).

In 1962 they took 3 months' study leave to the Ionic Research Unit (IRU) in the Department of Physiology, University of Melbourne, headed by the renowned RD Wright. The IRU was home to the transplanted adrenal gland in sheep. With this preparation, it was uniquely possible to study aldosterone biosynthesis in the conscious animal.

'There was an annoying residue that seemed to contain something with a quite different activity, concerned with sodium and potassium balance'

The Tait's returned to London in 1970, where James and Sylvia were joint Heads of the Biophysical Endocrine Unit in the Department of Physics as Applied to Medicine at Middlesex Hospital Medical School; James was also Professor and Head of Department. They continued to work on regulation of steroid secretion from isolated and purified adrenal cells, and later these methods were successfully applied to other cell types, including cardiac cells.

On retirement in 1982, James continued his work on adrenal cells and on the binding of steroid hormones to protein in blood. But it is undoubtedly the aldosterone work of the 1950s for which the Tait's will primarily be remembered.

JOHN P COGLAN
GAVIN P VINSON

This article has been reproduced in amended form with the kind permission of The Independent from an article that appeared on 21 February 2014.

CELEBRATING 15 YEARS: THE TURNER SYNDROME SUPPORT SOCIETY

After 15 years, the Turner Syndrome Support Society (TSSS) continues towards its goals of providing lifelong support and guidance to girls and women with Turner syndrome, raising awareness of this condition and encouraging early and timely diagnosis.



It is estimated that some 10,000 women and girls with Turner syndrome in the UK remain undiagnosed and therefore untreated. Lack of diagnosis and treatment may have profound physical and psychological effects. With this in mind, the TSSS has striven to raise awareness, so that women and girls can receive the treatment and care required to manage their condition. Even now, women are still contacting us or arriving at a clinic for the first time unaware of their needs, and there are still many more women to be found who need help.

The TSSS's membership continues to grow, and we are reaching more women and girls, resulting in them receiving invaluable medical treatment and emotional support. It is not overstating the case that we, as a society, have seen lives changed by this work.

SUPPORT NETWORK

We now have 12 active friendship groups located around the country that arrange a wide variety of activities from shopping and days out to Christmas parties, plus much else besides! It's also a great way for people to keep in touch, make friends and share experiences.

We are very fortunate to have a fantastic team of fundraisers who regularly donate money to the TSSS, and also very importantly contribute to raising awareness of Turner syndrome. For our 15th anniversary we are promoting T555 Club Fifteen: a whole year of raising funds and awareness.

The TSSS also publishes a newsletter called *ASPECTS* three times a year, which is circulated to members and the medical profession.



EVENTS AND PROFESSIONAL LINKS

Our annual conference and open days in various locations prove to be very popular and well supported. Many of the professionals who attend have commented on how they feel they have benefited from their contact with the TSSS, and welcome the chance to hear questions and views expressed during talks and workshops. This dual relationship – the way that medical professionals and a support society can work together for the benefit of the patients – is not widely known among the public.

The TSSS is very grateful for the provision of a free stand at this year's Society for Endocrinology BES conference, and for the opportunity to talk to and share information with endocrinologists dealing with Turner syndrome in relaxed and informal surroundings. The close monitoring of Turner syndrome patients by endocrinologists can help highlight the risks of aortic dissection and diabetes. We are very proud of our links with the medical profession and our thriving relationship with doctors and specialists.

With grateful thanks for a grant from the Society of Endocrinology, the TSSS has also been able to produce a new factsheet series, covering a wide range of issues confronted by women and girls with Turner syndrome.

NEW INTERNATIONAL GROUP

We are delighted to announce that Arlene Smyth, the TSSS's Executive Officer, is the President of the newly established International Turner Syndrome Group. A website is being established to bring together Turner syndrome societies worldwide. It was launched on 1 May 2014 at www.tsint.org. We aim to improve communications and provide accurate information for all to use – further details will follow in TSSS's next newsletter.

TIME TO CELEBRATE

Finally, the TSSS now has a membership of over 800 with many set to descend on Park Hall Hotel, Chorley, in October 2014 for a spectacular 15th Anniversary Crystal Ball and Annual Conference. This conference will highlight how a support society and the medical profession can work together in staging a fun celebration with the ability to pass on and share up to date accurate information through formal and informal meetings and gatherings.

We eagerly await the next 15 years!

JULIE CHAMPION AND ARLENE SMYTH
Turner Syndrome Support Society

CONTACT DETAILS FOR PATIENTS

- Telephone: 0141 952 8006
- Helpline: 0300 111 7520
- Email: turnersyndrome@tss.org.uk
- Web: www.tss.org.uk
- Facebook: www.facebook.com/TSSSUK
- Twitter: @turnersyndsoc

IMAGES IN ENDOCRINOLOGY

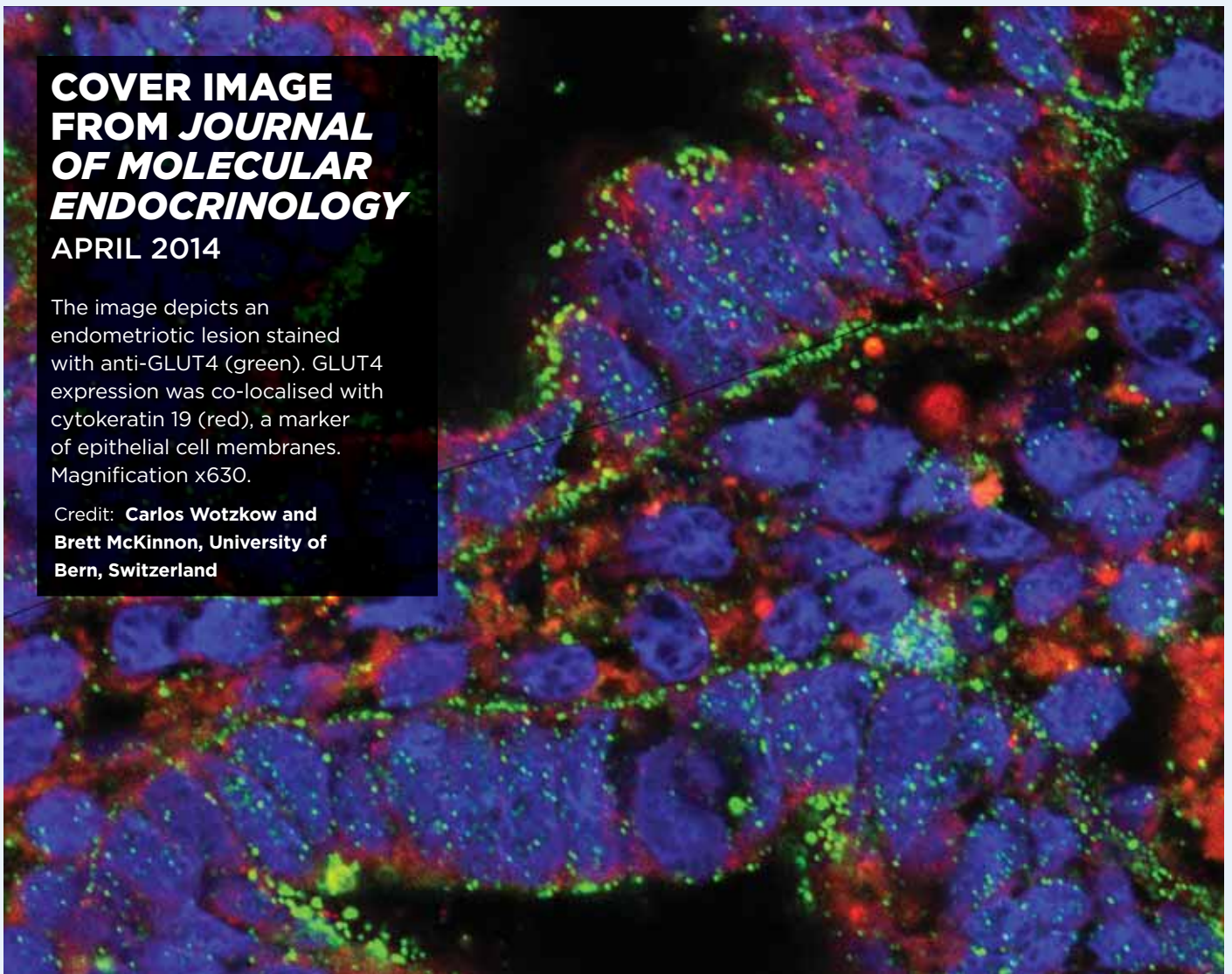
Here are the latest highlights from our journal Cover Art Competition, showcasing the best images in endocrinology.

COVER IMAGE FROM JOURNAL OF MOLECULAR ENDOCRINOLOGY

APRIL 2014

The image depicts an endometriotic lesion stained with anti-GLUT4 (green). GLUT4 expression was co-localised with cytokeratin 19 (red), a marker of epithelial cell membranes. Magnification x630.

Credit: **Carlos Wotzkow and Brett McKinnon, University of Bern, Switzerland**



Enter our Cover Art Competition

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

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FOR MALE HYPOGONADISM WITH CONFIRMED TESTOSTERONE DEFICIENCY¹

TOSTRAN[®] CONVENIENT BY DESIGN

METERED DOSE FOR ACCURATELY
DISPENSING THE CORRECT AMOUNT
(ENABLING INDIVIDUAL DOSE TITRATION)¹

QUICK DRYING GEL MEANS
PATIENTS CAN SHOWER
2 HOURS AFTER
APPLICATION¹

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/hypercalcuria. 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 60g 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

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