THE ENDOCRINOLOGIST
THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

From genetics to therapeutics: THYROID COVERED

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www.endocrinology.org/endocrinologist
A word from THE EDITOR...

After going a bit left field and geopolitical in the last issue, time to return to the endocrine pantheon and dedicate an issue to that quintessential endocrine organ, the thyroid. The prevalence of thyroid disorders, the relative ease with which it can be physically examined and imaged and the inability of anyone to enter a hospital department for anything without having a TSH measured, means the workings of this gland are familiar to many.

But do not let this familiarity breed contempt because there are still challenges and important unanswered questions and we are here to help. For jobbing clinicians faced with the question ‘T3 or not T3?’ on a daily basis, help is at hand with concise and hugely informative piece from Mark Vanderpump. For those who wonder if there may ever be something better out there than repeat prescriptions, look to Tony Hollenberg’s article on the exciting and rapidly progressing field of thyroid regeneration. Vicki Smith takes us through the science behind emerging therapies for radioiodine refractory thyroid cancer while Nadia Schoenmakers keeps us up to speed on the mechanistic detail underlying congenital hypothyroidism. Also, read Joe Straw’s story on his struggles with this condition as a reminder of how things can all too easily go awry.

Articles on Clinical Research Networks from John Wilding and a successful Society sponsored meeting from Paul Foster and Jonathan Wolf Mueller again speak to the power of working together to be more than the sum of the parts. We also shamelessly roll our own log and show off the best of what is coming up for jobbing clinicians faced with the question ‘T3 or not T3?’ on a daily basis, help is at hand with concise and hugely informative piece from Mark Vanderpump. For those who wonder if there may ever be something better out there than repeat prescriptions, look to Tony Hollenberg’s article on the exciting and rapidly progressing field of thyroid regeneration. Vicki Smith takes us through the science behind emerging therapies for radioiodine refractory thyroid cancer while Nadia Schoenmakers keeps us up to speed on the mechanistic detail underlying congenital hypothyroidism. Also, read Joe Straw’s story on his struggles with this condition as a reminder of how things can all too easily go awry.

Talking of ‘the best’, I finish with the sad news that Jennie Evans is moving on from her current position as Managing Editor on The Endocrinologist to exciting pastures new. She won’t say it herself so I will; Jennie has been the real engine at the heart of this magazine and has been an absolute joy as a colleague, remaining good humoured, patient and energetic however behind or disorganised the rest of us seem to be. I know she will be missed by all at the Society and we wish her only good things for the future. Thanks Jennie!

See you all in Harrogate this November.

BEST WISHES

TONY COLL

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

We congratulate Andrew Hattersley, Professor of Molecular Medicine at the University of Exeter, whose work on the genetic causes of diabetes has been recognised by the award of an OBE for services to medical science.

We’re honoured that Andrew will give the Dale Medal Lecture entitled ‘Diagnostic diabetes: a paradigm shift’ at the Society for Endocrinology BES conference on 7 November in Harrogate.

ARE YOU ON ANOTHER SOCIETY’S COMMITTEE?

DO YOU HOLD A POSITION IN A FUNDING BODY?

The Society for Endocrinology is interested in identifying people who hold a position on any other societies’ committees or have a post within a funding body, particularly those related to collaborative medical research, including National Institute for Health Research Commissioning Committees. If this applies to you, please contact Julie Cragg at members@endocrinology.org.

FAREWELL TO RACHEL

In October, we say farewell to Rachel Evans, who has worked for the Society for nearly 14 years.

For much of this time, she has headed up the Society’s Membership & Professional Affairs team and seen many changes take place – not least working with three Chief Executives and six different sets of Officers. She has made a huge contribution to driving the Society onward and upward. All of this was delivered with sound judgement, inimitable style and her own very special brand of humour.

We will miss her enthusiasm very much and wish her all the very best in her new endeavours.

CLINICAL EXCELLENCE AWARDS: CALL FOR PANEL MEMBERS

The Society seeks new members to join its Clinical Excellence Awards Panel. Panel members work with the Society office to rank applications and write citations. Typically, 12 applications per year are shared amongst 6 panel members.

If you are a Platinum, Gold or A+ Clinical Excellence Award holder who would like to support others who are applying for awards, please contact members@endocrinology.org, marking your email FAO Julie Cragg.

UPDATES AT THE ENDOCRINOLOGIST

After 4 years, Jennie Evans is stepping down from her position as Managing Editor of The Endocrinologist. Our grateful thanks to her for all her work and input to the magazine during this time.

We’re delighted to welcome Eilidh McGregor as the new Managing Editor and she will take over from the next issue onwards. If you would like to contact Eilidh, please email endocrinologist@endocrinology.org

JOURNAL IMPACT FACTORS

It’s been another fantastic year for the Society’s journals’ impact factors!

Endocrine Connections, our open-access journal, has received a remarkable first impact factor of 2.541 – a testament to the high quality of the published articles and the hard work of the editorial board, including the late Editor-in-Chief, Jens Sandahl Christiansen.

For another year, Journal of Endocrinology’s impact factor has continued to increase, reaching 4.706.

Journal of Molecular Endocrinology’s impact factor has increased to 3.577, making it the leading journal dedicated to molecular endocrinology.

Endocrine-Related Cancer has received an impressive impact factor of 5.267, its highest since 2003.

Clinical Endocrinology has received a strong impact factor of 3.327.

Our thanks go to the journals’ Editorial Boards and publishing team for their commitment and to you for supporting the Society’s journals.

SOCIETY CALENDAR

6-8 November 2017
SIE BES CONFERENCE
Harrogate

12 March 2018
SIE NATIONAL CLINICAL CASES MEETING
London

16-17 April 2018
ENDOCRINE NURSE UPDATE
Birmingham

16-18 April 2018
CAREER DEVELOPMENT WORKSHOP
Birmingham

16-18 April 2018
CLINICAL UPDATE
Birmingham

www.endocrinology.org/events for full details

SOCIETY SUPPORTED EVENTS

27 February-2 March 2018
NUCLEAR RECEPTORS: NEW ROLES FOR NUCLEAR RECEPTORS IN DEVELOPMENT, HEALTH AND DISEASE
Cancun, Mexico

GRANT AND PRIZE DEADLINES

30 September 2017
PUBLIC ENGAGEMENT GRANTS

31 October 2017
PRACTICAL SKILLS GRANTS

27 November 2017
EARLY CAREER GRANTS

27 November 2017
EQUIPMENT GRANTS

27 November 2017
ENDOCRINE NURSE GRANTS

15 December 2017
TRAVEL GRANTS

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

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Common vices of men and the health of the next generation

Paternal traits, such as advanced age, smoking and stress, can ‘programme’ changes in offspring, leading to an increased risk of neurological, behavioural and/or metabolic disease in later life.

In this review, Fullston et al. have focused on the impact of the three most prevalent vices among men (alcohol consumption, overweight/obesity and tobacco smoking), which are leading risk factors for death and disability adjusted life years worldwide. They have examined their effect on the function and molecular composition of sperm as well as longer term offspring health.

They have also highlighted prime candidate mechanisms involved in the non-genetic [i.e. epigenetic] paternal transmission of disease risk to the offspring.

Age-related changes in macaque arcuate nucleus gene expression

The arcuate nucleus is a major centre of control for reproduction. While most studies on this topic focus on gene changes in puberty, Eghlidi et al. profiled the aged arcuate nucleus.

Using microarrays, they compared the expression profiles of young and aged male arcuate nuclei, obtained from rhesus macaques. Although no significant changes in gene expression were noted from microarray data, qPCR (quantitative polymerase chain reaction) showed age-related decreases in progesterone receptor and androgen receptor expression. This study also found differences in kisspeptin and neurokinin B expression in aged males versus females, highlighting some previously undescribed sexually dimorphic arcuate nucleus gene expression with ageing.

Read the full article in Journal of Endocrinology 234 F1–F6

A role for TET2 in parathyroid carcinoma

Parathyroid carcinoma (PC) is a slow-growing and rare parathyroid disease. Recent studies have suggested a role for epigenetic modulation (e.g. DNA methylation and 5-hydroxymethylation) in PCs. Decreased levels of 5-hydroxymethylcytosine (5hmC) have been shown to be associated with downregulation of the ten-eleven translocation (TET) family of proteins in a wide variety of cancers. TET proteins oxidise 5-methylcytosine to 5hmC.

In this study, Barazeghi et al. presented data which suggested deregulated expression of TET2 by promoter hypermethylation in PC. PCs from patients showed very low TET2 protein abundance. Additionally, in vitro experiments in parathyroid cells showed a growth suppressive role for TET2, suggesting an important role for TET2 in parathyroid tumorigenesis. Interestingly, TET2 knockdown was found to interfere with the regulation of cell migration in vitro, resulting in increased migration.

The authors also determined TET2 Cpg island methylation by quantitative bisulphite pyrosequencing analysis and found an increased CpG methylation level in PCs compared with normal parathyroid tissues. They suggested, however, that other inactivating mechanisms, in addition to DNA methylation, must be involved, since one of the PC samples showed obvious low methylation levels throughout the region.

Read the full article in Endocrine-Related Cancer 24 329–338

How androgens regulate bird song

The neural basis for the alteration of learned vocalisations through development and adulthood is known to be related to the action of sex steroid hormones. Using male canaries (Serinus canaria) as a model, Alward et al. examined how steroid signalling in the brain affected particular features of their song. Male canaries are a good model for this type of study, as they show extensive vocal plasticity throughout life, paralleling vocal development in humans.

By blocking androgen receptors in two key brain regions involved in singing – the robust nucleus of the accumbens and the HVC – the researchers were able to tease out which aspects of song were affected. Androgens in the HVC were found to affect song variability, including how often the birds used a particular syllable, the order of syllables and the duration of trills. Meanwhile, androgens in the accumbens regulated the syllable and trill bandwidth.

These results show that androgen signalling has precise effects in the canary brain, regulating distinct features of complex motor output in an exact and non-redundant manner.

Read the full article in Journal of Neuroscience doi:10.1523/JNEUROSCIS.3371-16.2017
New tool to help diagnose malignancy in PPGL patients

There is currently no single histological or molecular marker to diagnose malignant phaeochromocytomas and paragangliomas (PPGLs). This study by Zhong et al. is the first to describe the development and validation of a prognostic nomogram to predict malignancy in patients with PPGL. Using a dataset of 347 PPGL patients (randomly divided into a training set (n=208) and a validation set (n=139)) and multivariate logistic regression analysis, the team developed a nomogram based on routinely available clinical variables (such as primary tumour size and location, catecholamine type, vascular invasion) and biomarkers (SDHB mutation and ERBB-2 expression) to predict the likelihood of malignancy from PPGLs in individual patients. The nomogram showed good calibration and discrimination capabilities. The authors hope that it can be used by clinicians to enhance their ability to assess patient prognosis and strengthen prognosis-based decision making.

Read the full article in Clinical Endocrinology 87 127–135

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Challenges presented by parathyroid carcinoma with multiple lung metastases

Parathyroid carcinoma is a rare malignancy, accounting for less than 1% of patients with primary hyperparathyroidism. The hyperparathyroidism is usually more severe than that seen in benign disease. This case highlights a diagnostic challenge due to the absence of reliable criteria for parathyroid carcinoma. Rozhinskaya and colleagues describe the case of a 27-year-old woman whose initial misdiagnosis of a parathyroid carcinoma led to the development of multiple lung metastases. They further emphasise the importance of thorough histological examination using immunohistochemical staining of resected tissue in suspicious cases.

Read the full article in Endocrinology, Diabetes & Metabolism Case Reports EDM160113

ENDOCRINE CONNECTIONS

Quality of life in women with congenital hypogonadotrophic hypogonadism

This study by Dziemał et al. of quality of life in women with congenital hypogonadotrophic hypogonadism (CHH) is striking for a number of reasons. These include the delays reported in diagnosis and access to specialist care, the long gaps in treatment experienced by more than half of patients, the variability found in availability of genetic testing and the low rate of discussion of CHH’s psychological impact.

Just 25% of patients felt that their healthcare provider understood how patients felt when living with CHH, and 27% were offered referral to psychological services. Additionally, only 38% were offered fertility treatment. Of these, 89% were able to conceive, so it appears that many women were not offered fertility treatment, which has a good success rate in this patient group.

Read the full article in Endocrine Connections 6 404–412

Can osteocalcin reverse age-related memory decline?

Osteocalcin (OCN), an osteoblast-specific hormone, is known to perform multiple functions within the body, including a role in hippocampal-dependent memory and the prevention of anxiety-like behaviours. Using a murine model, Khrimian et al. set out to discover whether OCN can improve these behaviours in older individuals; i.e. could this hormone facilitate the reversal of age-related memory loss?

Aged mice (16 months old) significantly improved their performance on two different memory tests when given continuous infusions of OCN over a 2-month period, reaching levels usually only observed in younger animals. Similar results were obtained when blood plasma from young mice, rich in OCN, was injected into aged mice. Following this, the team set out to identify the neurone receptor to which OCN binds. They identified Gpr158, a receptor abundant in particular regions of the hippocampus, the brain’s memory centre. Subsequent tests revealed that mice with inactivated hippocampal Gpr158 did not have improved memory tests when given OCN.

Overall, the results reveal an intriguing role for OCN in age-related cognitive decline, paving the way for a novel line of enquiry for treating this type of condition.

Read the full article in Journal of Experimental Medicine doi:10.1084/jem.20171320

The world’s oldest known case of gigantism?

Gigantism and acromegaly are conditions that have been recorded by physicians throughout history. In this short correspondence, Galasić et al. claim to have identified the world’s oldest known case of gigantism, in a Third Dynasty Egyptian pharaoh who ruled more than 4,700 years ago.

In their study, the team analysed the remains of a man who was 187cm tall, purported to be King Sa-Nakht, who ruled in the Third Dynasty. The skeleton was originally excavated from the Mastaba K2 tomb near Beit Khalaf in Egypt in 1901. By assessing previously recorded measurements of the skull and carrying out a comparison with anthropological databases, as well as reviewing photographs of the skull, the team concluded from the signs of exuberant growth on his long bones that the man probably had gigantism. If confirmed, this would represent the oldest known palaeopathological case of gigantism in the world.

Read the full article in The Lancet Diabetes & Endocrinology 5 380–381

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TEAMeD (Thyroid Eye Disease Amsterdam Declaration Implementation Group UK) was established in 2009 to implement the Amsterdam Declaration, which pledged to improve care for people with TED and prevent TED in those at risk. This autumn, TEAMeD is launching ‘TEAMeD-5’, a campaign to promote better care for patients with, or at risk of, TED. This campaign seeks to promote five recommendations in TED management (Figure 1).

Thyroid eye disease (TED) is a distressing complication of Graves’ disease. TED can have a significant and negative impact upon the quality of patients’ lives and visual function. Delays in making a diagnosis of TED and initiating treatment are common. A recent study has shown that the median time from first symptoms to a diagnosis of TED is 7 months, and the median time from first visit to any doctor with symptoms to diagnosis is 2 months.1

1. DIAGNOSE GRAVES’ DISEASE ACCURATELY

Measure TSH (thyroid-stimulating hormone) receptor antibody (TRab)

Graves’ disease, the most common cause of hyperthyroidism in the UK, is caused by autoantibodies to the TSH receptor (TRab). Reliable, low cost TRab assays are available and can diagnose Graves’ disease with >95% sensitivity and specificity. A positive TRab test in the context of thyrotoxicosis identifies those at risk of TED, with higher TRab levels being associated with greater TED incidence and severity. TRab testing is still not routine in the diagnosis of thyrotoxicosis in many parts of the UK. However, using this test in all thyrotoxic patients is strongly recommended in order to target TRab-positive individuals with measures to increase awareness and reduce the risk of TED (see TEAMeD-5 points 2–4 below). Patients without circulating TRab are at very low risk of TED.

KEY RECOMMENDATION
TEAMeD recommends that an accurate diagnosis of the cause is made in all cases of thyrotoxicosis to determine the risk of TED; TRab testing is a useful tool in the diagnosis of Graves’ disease.

2. SCREEN ALL GRAVES’ PATIENTS FOR TED

Use the DiaGO clinical assessment tool

It can be challenging for endocrinologists to recognise TED and decide who should be referred for ophthalmic care. TEAMeD has developed DiaGO, a clinical assessment tool to screen all patients with Graves’ disease for signs and symptoms of TED, for use in general endocrinology clinics.2 DiaGO comprises 20 yes/no questions which aim to elicit signs and symptoms of TED. DiaGO has been tested and was found to be highly sensitive in picking up TED with a low false-positive rate (<8%). Half the individuals referred to the specialist clinic were offered ophthalmic treatment. This suggests that use of the tool is actively altering management in patients who might otherwise have been referred and treated. DiaGO is easy to use (it can be completed in less than 5 minutes) and does not require specialist ophthalmic skills.

KEY RECOMMENDATION
TEAMeD recommends a systematic assessment for early signs/symptoms of TED in all patients reviewed in endocrine clinics with an established diagnosis of Graves’ disease. This permits prompt and timely referral to appropriate ophthalmic care.

3. ALERT ALL GRAVES’ PATIENTS TO THE RISK OF TED

Give patients TEAMeD Early Warning Cards

Increasing awareness of the early signs of TED in all patients with Graves’ disease aims to reduce delays in presentation and diagnosis. TEAMeD has developed TEAMeD ‘Early Warning Cards’, which can be given to all patients with an established diagnosis of Graves’ disease (but currently without TED), to raise awareness of TED and to facilitate earlier diagnosis (Figure 2; www.btf-thyroid.org/images/documents/S5.pdf). The Early Warning Card describes common symptoms of TED and has space for a local telephone number which can be contacted by individuals with concerns. In patients with Graves’ disease but without TED at baseline, the incidence of TED is expected to be approximately 15% per annum. In a pilot study of 160 patients who were issued with TEAMeD Early Warning Cards, 6% contacted their endocrine service about new eye symptoms.

KEY RECOMMENDATION
TEAMeD recommends that all patients with Graves’ disease are informed about the risk of TED and given an Early Warning Card, as shown in Figure 2.

4. PREVENT TED

Encourage smoking cessation
Achieve and maintain euthyroidism rapidly
Avoid hypothyroidism after 131I
Avoid 131I in active TED

Current smoking is the strongest risk factor for developing TED.3 Patients with Graves’ disease who smoke are approximately five times more likely to develop TED than non-smokers, and smokers tend to have more severe disease than non-smokers.4 There is evidence for a dose–response relationship between smoking and the severity of TED.5 Smoking cessation advice should be given to all Graves’ disease and TED patients who are current smokers and they should be referred to smoking cessation services for support with quitting. TEAMeD has developed a web-based smoking

Figure 1. TEAMeD-5: five steps to improve outcomes in TED patients.

TEAMeD-5: IMPROVING OUTCOMES IN THYROID EYE DISEASE

WRITTEN BY MOHD SHAZLI DRAMAN, ANNA MITCHELL & COLIN DAYAN

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Figure 1. TEAMeD-5: five steps to improve outcomes in TED patients.
Thyroid dysfunction (untreated hyperthyroidism and hypothyroidism) is associated with an increased risk of severe TED.12 Radioactive iodine treatment (131I) is associated with worsening of existing TED and an increased risk of developing TED de novo, in the order of 15–30%.7 In addition, 121I results in a period of hypothyroidism in up to 60% of individuals,8 which can trigger or exacerbate TED.

Clinicians should focus on preventing hypothyroidism (which is inevitable in the majority of patients post-131I), by timely introduction of levothyroxine replacement. Thyroid function tests should be undertaken every 1–2 months for the first 6 months, beginning no later than 4 weeks after treatment. Effective communication between specialist, patient and family doctor is key. Levothyroxine should be introduced when free thyroxine levels are low or showing a downward trend within the normal reference range, even in the absence of raised TSH, as the rise in TSH may be transient. If 131I cannot be delayed, steroid cover is required.9 See the BOPSS website at www.bopss.co.uk.

Mild TED
TED which only has a minor impact on daily life and quality of life can be described as mild TED. A TEAMeD factsheet about the recognition and management of mild TED is available (http://bit.ly/2xGlFvE). It outlines simple and effective strategies which should be offered to patients, including a 6-month course of sodium selenite at a dose of 100g twice daily (equivalent to a total daily dose of 91.3µg of elemental selenium) and topical lubricants (artificial tears and ointments). Patients with Graves’ disease hyperthyroidism with mild TED can be managed by an endocrinologist with an interest in TED.

Moderate–severe or referable TED
All patients with moderate to severe TED (patients with sight-threatening TED, diplopia or whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression or surgical intervention), those with mild TED that progresses and those whose TED has a significant impact upon their quality of life, regardless of severity, should be referred to a joint multidisciplinary thyroid eye clinic. Early expert management of active TED has the potential to improve long term outcomes. Patients with new or recent-onset visual impairment should be referred urgently and seen within 2 weeks.

TEAMeD has collaborated with the British Oculoplastic Surgical Society (BOPSS) to develop defining criteria for a specialist service, and agreed audit standards. To avoid delays in this complex disease and to optimise outcomes, it is recommended that all patients with referable TED are referred directly to a specialist clinic. Key elements of a specialist TED service include a joint service with endocrinology and access to all surgical (decompression, strabismus correction and oculoplastic surgery) and immunomodulatory expertise that may be required.8 See the BOPSS website at www.bopss.co.uk.

KEY RECOMMENDATION
TEAMeD recommends that endocrine teams identify a specialist multidisciplinary thyroid eye clinic in their region consistent with BOPSS recommendations, and refer all patients with moderate or severe TED or TED affecting the patients’ quality of life to this service.

TEAMeD-5 will be officially launched at the Society for Endocrinology BES conference in November. To find out more about TEAMeD-5, see www.btf-thyroid.org/teamed-5.

MOHD SHAZLI DRAMAN, ANNA MITCHELL & COLIN DAYAN on behalf of TEAMeD (Thyroid Eye Disease Amsterdam Declaration Implementation Group UK)

REFERENCES

5. REFER TO A SPECIALIST CLINIC EARLY
Refer patients with moderate or severe TED, or TED which affects their quality of life, to a specialist multidisciplinary joint thyroid eye clinic

TEAMeD has published guidelines for the management of patients with TED,9,10 with an emphasis on early recognition and diagnosis.
Primary congenital hypothyroidism (CH) is the most common neonatal endocrine defect, and delayed diagnosis can result in significant neurodevelopmental impairment. The UK CH screening programme, which detects CH using a neonatal blood spot thyrotropin (TSH) measurement, has been resoundingly successful in negating requirements for special schooling for children with CH. However some CH patients may still exhibit subtle cognitive deficiencies.

Thyroid dysgenesis results in CH, due to complete failure of thyroid development (agenesis), ectopic development or (rarely) development of a hypoplastic but normally located thyroid gland. CH resulting from dysmorphogenesis may be gonadal, and occurs due to a specific defect in one of the components of the thyroid hormone biosynthetic machinery. Older studies, using TSH screening cut-offs of >20mU/l, attributed at least 80% of CH to thyroid dysgenesis. However, more recent studies, using lower TSH screening cut-offs, have found that most CH cases have a normally located thyroid gland in situ.

NORMAL DEVELOPMENT AND HORMONE BIOSYNTHESIS

Our understanding of normal thyroid physiology and development has been key to identifying genetic causes of CH.

During embryogenesis, a thyroid domain is specified in the foregut endoderm, close to the tongue base. Following evagination of a thyroid primordium, thyroid precursor cells migrate downwards, reaching their final position anterior to the trachea around 40 days post fertilisation. Terminal differentiation then begins with polarisation and adhesion of individual thyroid follicular cells to form functional follicles. Fetal thyroid hormones are detectable in the circulation around gestational week 12.

The figure below outlines the key molecules involved in thyroid hormone biosynthesis.

GENES KNOWN TO BE IMPLICATED IN CH

The majority of dysmorphogenesis is explained by mutations in key genes encoding components of the thyroid hormone biosynthesis pathway (Figure). Recessively inherited mutations in any of these molecules and dominantly inherited DUOX2, IYD and DUOX2 mutations have all been associated with CH or goitre (Table). Four key thyroid transcription factors mediate normal thyroid development: NKX2-1, PAX8, FOXE1 and HHEX. Their combined, co-ordinated expression defines developing thyroid follicular cells. Heterozygous NKX2-1 and BLG mutations and recessively inherited FOXE1 mutations are all associated with thyroid dysgenesis, and may also result in extrathyroidal phenotypes, reflecting individual roles of these transcription factors in the morphogenesis of additional organs (Table). Mutations in these genes are rare, accounting for 5% of CH (Table). Mono- or biallelic mutations in the TSHR gene cause a variable spectrum of TSH resistance, ranging from thyroid hypoplasia and severe CH to mild isolated hyperthyrotoxiaemia, with normal thyroid morphology. TSHR mutations are relatively common, accounting for up to ~20% of paediatric non-autoimmune hyperthyrotoxiaemia (Table). Collectively, <20% of CH is accounted for by known genetic causes, and the frequent sporadic occurrence of thyroid dysgenesis and high discordance rate in monozygotic twins has led to the hypothesis that thyroid somatic mutations account for thyroid dysgenesis. However, observations that 2% of thyroid dysgenesis is familial, and the enrichment of extrathyroidal developmental abnormalities in CH cases, support the existence of hitherto undiscovered genetic causes.

WHEN IS GENETIC ASCERTAINMENT IMPORTANT?

On receipt of a positive CH screening test result, parents invariably ask why their baby has CH. A confirmatory genetic diagnosis may answer this question, and facilitate genetic counselling and management of cases likely to exhibit syndromic features.
The genetic defects implicated in CH

<table>
<thead>
<tr>
<th>Gene</th>
<th>Biochemical severity of CH</th>
<th>Radiological features</th>
<th>Associations/significant features</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKX2-1</td>
<td>Euthyroid – severe</td>
<td>GIS – athyreosis</td>
<td>Neurological (e.g. BHC, -90% cases)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Respiratory (e.g. IRDS, &gt;50% cases)</td>
</tr>
<tr>
<td>PAX8</td>
<td>Euthyroid – severe</td>
<td>Typically hypoplasia</td>
<td>Urogenital tract malformations (rare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GIS – athyreosis</td>
<td></td>
</tr>
<tr>
<td>FOXE1</td>
<td>Severe</td>
<td>Athyreosis</td>
<td>Cleft palate, spiky hair (universal), choanal atresia</td>
</tr>
<tr>
<td>TSHR</td>
<td>Subclinical – severe</td>
<td>GIS – severe hypoplasia</td>
<td>TSH resistant</td>
</tr>
<tr>
<td>TG</td>
<td>Euthyroid – severe</td>
<td>GIS – goitre</td>
<td>May cause fetal goitre</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thyroglobulin low/normal despite high TSH</td>
</tr>
<tr>
<td>TPO</td>
<td>Usually severe</td>
<td>GIS – goitre</td>
<td>May cause fetal goitre</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIOD</td>
<td></td>
</tr>
<tr>
<td>DUOX2</td>
<td>Mild–severe</td>
<td>GIS – goitre</td>
<td>CH may be transient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIOD</td>
<td>Borderline screening TSH result, significantly elevated TSH at time of confirmatory testing</td>
</tr>
<tr>
<td>DUOXA2</td>
<td>Mild</td>
<td>GIS – goitre</td>
<td>CH may be transient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIOD</td>
<td></td>
</tr>
<tr>
<td>SLC26A4 (pendrin)</td>
<td>Euthyroid – mild</td>
<td>GIS – goitre</td>
<td>Sensorineural hearing loss, EVA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIOD</td>
<td></td>
</tr>
<tr>
<td>NIS/SLC5A5</td>
<td>Euthyroid – severe</td>
<td>GIS – goitre</td>
<td>Presentation may be delayed resulting in neurodevelopmental delay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased thyroid $^{125}$I/Tc uptake</td>
<td></td>
</tr>
<tr>
<td>IYD</td>
<td>Euthyroid – severe</td>
<td>Goitre</td>
<td>Raised urinary MIT and DIT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Presentation may be delayed resulting in neurodevelopmental delay</td>
</tr>
</tbody>
</table>

BHC, benign hereditary chorea; DIT, di-iodotyrosine; EVA, enlarged vestibular aqueduct; GIS, normally located thyroid gland in situ; IRDS, infant respiratory distress syndrome; MIT, mono-iodotyrosine; PIOD, partial iodide organification defect; Tc, technetium; TIOD, total iodide organification defect.

It may enable cases of likely transient CH to be identified (usually due to DUOX2 or DUOXA2 mutations), informing a trial of levothyroxine withdrawal. Additionally, CH with certain genetic aetiologies (NIS, IYD, DUOX2 mutations) may present with normal neonatal TSH levels but evolve to significant hypothyroidism in later childhood. A falsely reassuring CH screening result in such cases may lead to delayed diagnosis with adverse sequelae. However, genetic ascertainment may promote early biochemical surveillance of affected siblings.6,7

TSHR mutations may cause resistance to TSH, resulting in persistently elevated TSH despite high/high normal free thyroxine. However, levothyroxine treatment may not be required for normal growth and development, and attempts to normalise TSH may provoke thyrotoxic symptoms. Detection of a TSHR mutation in such cases may therefore aid clinical management by permitting a more appropriate (higher) TSH target range to be agreed.8

LESSONS FROM NEXT GENERATION SEQUENCING

Next generation sequencing technologies have demonstrated a role for oligogenicity in the pathogenesis of CH, which may explain the variable penetrance observed.9,10 Whole exome sequencing in familial cases has identified mutations in borealin (CDCA8) as a novel monogenic cause of thyroid dysgenesis.11 Additionally, association of mutations in known genes with unexpected thyroid morphology (e.g. pendrin (SLC26A4) in thyroid dysgenesis) has broadened our perspective on the phenotypes associated with particular genetic mutations.12 It remains to be seen whether further studies, including those using whole genome sequencing, will identify additional genetic causes in known or novel candidate genes.

NADIA SCHOENMAKERS

Wellcome Intermediate Clinical Fellow & Honorary Consultant Endocrinologist, University of Cambridge Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, Addenbrooke’s Hospital, Cambridge

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1. Rovet JF 2005 Pediatrics 115 e52–e57.
LITHYRONINE (L-T3) TREATMENT IN HYPOTHYROIDISM

WRITTEN BY MARK VANDERPUMP

Over 1 million people in the UK take levothyroxine sodium (L-T4). The goal of therapy is to restore patient well-being and normalise serum thyrotrophin (TSH) levels. Most patients respond satisfactorily, but a minority of treated individuals experience persistent symptoms despite adequate biochemical correction. The care of such individuals is challenging and remains the subject of considerable public interest.

A HISTORICAL PERSPECTIVE

Synthetic forms of L-T4, available since the 1950s, were introduced without any consideration of the need for randomised controlled trials. The existing porcine thyroid extracts were far from physiological, as the pig thyroid produces thyroxine (T4) and tri-iodothyronine (T3) at a ratio of 4:1, compared with the ratio of 14:1 in human thyroid.

Evidence appeared of potential harm from L-T4 over-replacement, including atrial fibrillation and bone loss, particularly in postmenopausal women. More accurate serum TSH measurement meant that patients were prescribed lower doses of L-T4 than in earlier decades, which were more closely matched to their serum TSH, T4 and T3 levels.

THE USE OF COMBINATION THERAPY

Data available on 1,355 patients in 13 randomised controlled trials of L-T4+L-T3 (liothryronine) versus L-T4 monotherapy reveal insufficient evidence that combination treatment is more effective than monotherapy.

Endocrinologists should rule out autoimmune disease associated with thyroid autoimmunity, reassure patients about their condition and support them in coming to terms with a chronic disease requiring lifelong medication. If symptoms still persist for 6 months or more, some endocrinologists will consider combination treatment on an experimental basis.

‘Sudden withdrawal of L-T3 therapy is not supported, as clinical need should come before financial considerations.’

In 2016 the British Thyroid Association (BTA) published a statement endorsed by the British Thyroid Foundation and the Society for Endocrinology on current best practice for the management of primary hypothyroidism. A decision to embark on a trial of L-T4/L-T3 combination therapy in patients who have unambiguously not benefited from L-T4 should be reached following an open and balanced discussion of the uncertain benefits, likely risks of over-replacement and lack of long term safety data. Such patients should be supervised by accredited endocrinologists with documentation of agreement after fully informed and understood discussion.

L-T3 AVAILABILITY

Recently, many patients have been informed of a lack of L-T3 availability on the basis of cost. The price increase in L-T3 has arisen because generic products in the NHS are not price-controlled to encourage competitive pricing and keep prices down. However, this can have the opposite effect where there is a limited number of suppliers for a product, as suppliers can choose to increase prices unilaterally.

Several years ago, L-T3 became generic with a single supplier, Goldshield, which became AMCo, and now Concordia. There has been a gradual price increase, particularly in the last 3 years, and this increase appears to have occurred more notably in the UK relative to other European countries. The Competition and Markets Authority (the competition watchdog) has investigated and is due to report shortly.

WITHDRAWING OR INTRODUCING L-T3

Sudden withdrawal of L-T3 therapy is not supported, as clinical need should come before financial considerations. For patients who are long established on L-T3 and are thought to be stable, a change to L-T4 monotherapy should not be implemented without careful discussion. In such cases, change of treatment may result in significant instability of thyroid status and potentially undesirable clinical outcomes, which may prove more expensive than continuation with L-T3 therapy.

For patients with hypothyroidism who are not on L-T3 but wish to be treated with L-T3, the principles in decision-making should be in accordance with those outlined in the BTA statement and in line with the best principles of good medical practice. Combination treatments of L-T3 and L-T4 should only be initiated and supervised by accredited endocrinologists.

In patients where it is agreed to switch from combined L-T3 and L-T4 treatment or from L-T3 monotherapy to L-T4 monotherapy, the transition should be made cautiously and gradually, aiming to avoid under- or over-replacement with thyroid hormones. The final L-T4 requirement is likely to be around 1.6µg/kg. Any information about previous L-T4 dosage that achieved a serum TSH within the reference range will be a useful guide that predicts the individual requirement.

Because of the long half-life of L-T4 and the short half-life of L-T3, a ‘one-step straight switch’ from L-T3 to L-T4 may result in a phase of under-replacement, especially in those previously treated with L-T3 monotherapy. Gradual reduction of L-T3 at the same time as introducing L-T4 may be a preferable alternative. Frequent assessment of clinical and biochemical thyroid status is recommended until stability is reached. Awareness of the pharmacokinetics of L-T3 and L-T4 is important in interpreting thyroid function tests during the transitional period.

In patients with thyroid cancer, where L-T3 is being recommended in preparation for radioiodine therapy or diagnostic imaging, access to L-T3 is imperative and substitution with L-T4 is inappropriate. L-T4/L-T3 combination therapy is not recommended in pregnancy, patients over the age of 60 or patients of any age with known heart disease, as additional care is required to avoid over-replacement. Desiccated animal thyroid extracts remain not recommended in the management of hypothyroidism.

MARK VANDERPUMP

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Mark Vanderpump is the former President of the BTA.

REFERENCE

THYROID REGENERATIVE THERAPY: NEW INSIGHTS

WRITTEN BY ANTHONY N HOLLENBERG

Since the 1890s, when George Redmayne Murray first used sheep thyroid extract, the principles of thyroid hormone replacement in hypothyroid patients have remained quite constant. The utilisation of pharmacologically produced thyroid hormones has vastly improved care, but considerable controversy still exists over the role of therapy with thyroxine (T4) and tri-iodothyronine (T3) together versus T4 alone in order to better mimic endogenous production. While better designed clinical trials in the future may improve exogenous thyroid hormone therapy, new advances in understanding thyroid development offer the potential to develop thyroid gland regeneration as an alternative for patients.

FOLLICULAR CELL DEVELOPMENT

The follicular cell of the thyroid is responsible for the synthesis of both T4 and T3. Its development from endoderm requires the expression of two transcription factors, Nkx2-1 and Pax8. Indeed, mutation of either leads to congenital hypothyroidism in humans. Interestingly, both Nkx2-1 and Pax8 are expressed in other cell types, but it is their co-expression in anterior endoderm that leads to the development of the follicular cell.

Clearly, factors required for thyroid gland development go well beyond these two proteins, and include a number of other transcription factors as well as the external milieu where the gland develops. Importantly, advances in embryonic stem cell (ESC) and induced pluripotent stem cell (iPSC) technology have had a significant impact on our understanding of follicular cell development and have opened up the future possibility of regenerative therapy for hypothyroidism.

In order to induce thyroid development from murine ESCs, investigators initially used a variety of techniques, including generating ESCs that possess a labelled thyrotrophin (TSH) receptor, so that cells poised to differentiate appropriately could be identified. While such techniques produced follicular-like structures in culture, it was not clear if they had the capacity to produce thyroid hormones.

CREATING FUNCTIONAL FOLLICLES

The first major breakthrough in this area was made by the laboratory of Sabine Costagliola, who co-expressed Nkx2-1 and Pax8 at a very early stage of mouse ESC development. By then adding TSH and providing a 3D culture system, these ESCs were able to develop into follicular structures that expressed thyroglobulin and also had the ability to take up iodine – a crucial step in thyroid hormone biosynthesis. More remarkably, when transplanted into athyreotic mice, these follicles fully functioned to restore normal thyroid hormone synthesis. These experiments proved that regenerative therapy for hypothyroidism was a possibility but, because of the transcription factor overexpression strategy employed, would probably not be clinically applicable.

To identify the actual differentiation pathway employed by ESCs or iPSCs to become follicular cells, our group has used a directed differentiation approach that uses growth factors thought to play a role in thyroid gland development in vivo. To enhance our ability to detect endodermal cells that are destined to become follicular cells, we labelled the Nkx2-1 locus with a fluorophore, such that cells appearing green or red could be identified. Using this technique we were able to identify that the growth factors bone morphogenic protein 4 (BMP4) and fibroblast growth factor 2 (FGF2) were absolutely required for endoderm derived from mouse ESCs to become thyroid follicular cells. Furthermore, both BMP4 and FGF2 appeared to play a similar role in Xenopus, suggesting that this pathway is conserved across species.

Once specified with BMP4 and FGF2, Nkx2-1 positive cells could then be further differentiated in a 3D culture system into follicular units that expressed all important thyroid markers, including thyroglobulin, and more importantly had the ability to synthesise small amounts of T4.
SEEKING SUCCESS IN VIVO
To prove these cells could function in vivo, we transplanted ESC-derived follicles after 30 days in culture into the kidney capsule of mice that had previously been given 131I to render them hypothyroid. At 2 weeks after transplantation, T4 began to reappear in the transplanted mice, and by 8 weeks almost all transplanted mice had become euthyroid. Importantly, the TSH set point returned to its pre-hypothyroid setting, demonstrating that the transplanted cells were entirely TSH-responsive.

Further testing showed that these cells could take up iodine and also be kept in place for a number of months without any abnormal growth. Thus, this protocol further demonstrated the possibilities for the development of regenerative therapy, using an approach that does not require modification of ESCs or iPSCs.

While the protocols developed using mouse ESCs have provided key insights into thyroid follicular cell development, the important next steps must occur in human ESC or iPSC models. Our group has shown that human iPSCs can be induced to express thyroid markers but, to date, functionality in vitro or in vivo is lacking. However, given the progress in the field, it is fully expected that a directed differentiation approach using human iPSCs should be possible and that transplantable follicles will be produced.

Clearly, the development of such cells from human iPSCs will only be the beginning of a long road of testing to determine whether such an approach could ever be used to repair hypothyroidism in our patients. Still these cells and the biologic processes that control their differentiation should provide ideal model systems to study the thyroid and its diseases for years to come.

ANTHONY N HOLLENBERG
Chief, Division of Endocrinology, Diabetes & Metabolism, Beth Israel Deaconess Medical Center and Professor of Medicine, Harvard Medical School

REFERENCES

THERAPEUTIC STRATEGIES IN RADIOIODINE REFRACTORY THYROID CANCER
WRITTEN BY VICKI SMITH

The usefulness of radioiodine ablation following surgery is a controversial subject. There is some debate about which patients with differentiated thyroid cancer (DTC) should receive it and at what dose. Most endocrinologists, however, would agree that the successful treatment of recurrent and metastatic disease with radioiodine is crucial for a good prognosis. Outcomes for advanced disease which no longer takes up radioiodine (radioiodine refractory DTC, RR-DTC) are often very poor, with dismal 10-year survival rates of <10%.

New systemic therapies for the treatment of RR-DTC, such as the tyrosine kinase inhibitors soferenib and lenvatinib, have recently shown genuine promise in clinical trials. The DECISION (soferenib) and SELECT (lenvatinib) phase 3 trials showed significantly improved progression-free survival. However, the considerable toxicities that are associated with these drugs may severely impact patients’ quality of life and ultimately become intolerable.

UNDERSTANDING RADIOIODINE UPTAKE
Another strategy for the treatment of RR-DTC is to restore radioiodine uptake in order to enable effective radioiodine treatment. This has highlighted a need to understand exactly how radioiodine uptake is regulated and how it is repressed in RR-DTC. Since the cloning of the sodium-iodide symporter (NIS) gene in 1996, we have known that this large transmembrane glycoprotein mediates radioiodine uptake. Its key regulator is thyroid-stimulating hormone (TSH), which induces both NIS expression and protein function, the latter by promoting membrane localisation. TSH levels are therefore boosted prior to radioiodine administration to enhance NIS function, either through induction of hypothyroidism following thyroid hormone withdrawal or by giving recombinant TSH. However, this is not effective in RR-DTC.

The driver mutation of the tumour plays a role in the loss of radioiodine uptake in RR-DTC; with mutated genes within the MAPK pathway (e.g. RET fusion, RAS) clearly associated with reduced uptake. In particular, the BRAFV600E mutation, found in ~60% of papillary thyroid cancers (PTC), is commonly found in RR-DTC and is known to inhibit the expression of iodide-metabolising genes including NIS. It is also linked with reduced NIS membrane localisation.

THERAPEUTIC APPROACHES
Consequently, in preclinical studies, MAPK pathway inhibitors have been effective in stimulating NIS expression and radioiodine uptake. This has led to a phase 2 clinical trial determining the effect of a MEK inhibitor, selumetinib, prior to radioiodine uptake in metastatic RR-DTC. Increased tumoural radioiodine uptake was seen in 60% of patients; in those with sufficient uptake for an ablative dose, tumour size was reduced and either a partial response or stable disease was observed. This study is certainly encouraging for the strategy of radioiodine uptake restoration, and a multicentre trial (SEL-I-METRY) is now underway in the UK to evaluate the use of selumetinib in RR-DTC.
‘The driver mutation of the tumour plays a role in the loss of radioiodine uptake, with mutated genes within the MAPK pathway clearly associated with reduced uptake.’

Although BRAF^{V600E} mutant tumours tended to respond poorly to pre-radioiodine selumetinib treatment, a similar trial in patients with BRAF^{V600E} mutations suggested that dabrafenib (a specific BRAF^{V600E} inhibitor) may be beneficial. More recently, the MEK inhibitor CKI, which sustains ERK inhibition, was found to be far better at restoring radioiodine uptake than selumetinib, which has a transient effect, although this is yet to be tested clinically.

Additional drug treatments are likely to be required for significant restoration of radioiodine uptake, particularly for BRAF^{V600E} mutant tumours. Potential targets include TGFβ (transforming growth factor-β), which is induced by BRAF^{V600E} and represses NIS through SMAD independently of the MAPK pathway. Recent data suggest this is mediated through reactive oxygen species (ROS) generated by NOX4, providing further possible targets. Other potential targets include the PI3K-AKT and NOTCH signalling pathways, as well as epigenetic alterations such as DNA hypermethylation and histone deacetylation. Redifferentiation using retinooids, PPAR-γ (peroxisome proliferator-activated receptor-γ) agonists and, more specifically, the modulation of miRNAs against key thyroid transcription factors such as PAX8 still warrant attention.

Correct targeting of NIS to the plasma membrane is essential for its function. Our work identified the first known molecule to interact with NIS and modulate its function. Pituitary tumour-transforming gene-binding factor (PBF) expression is upregulated in thyroid cancer and is induced by BRAF^{V600E}. PBF binds NIS and induces its internalisation. This interaction is mediated by PBF phosphorylation at Y174; the loss of phosphorylation through mutation or inhibition of the kinase responsible, Src, abrogates NIS–PBF binding. Src kinase inhibitors potently repress PBF-pY174 and prevent PBF-mediated repression of NIS. They therefore have potential clinical utility in restoring radioiodine uptake, particularly in the BRAF^{V600E} mutant tumours in which PBF is most highly expressed.

We are currently investigating two further novel interactors of NIS which modulate its function; ADP-ribosylation factor 4 (ARF4) and valosin-containing protein (VCP). ARF4 induces NIS function but is significantly downregulated in PTC. Conversely, VCP represses radioiodine uptake and is overexpressed in PTC. Both are under evaluation as potential targets for radioiodine restoration.

‘Our work identified the first known molecule to interact with the sodium-iodide symporter and modulate its function.’

It is likely that a combination of drug treatments will be required for maximum restoration of radioiodine uptake in RR-DTC. The ultimate pre-radioiodine treatment also has the potential for multiple applications. For example, it may be used to treat radioiodine-avid DTC and allow significant reduction in overall dosage and number of treatments. It may also increase the effectiveness of ablation and/or similarly allow a reduction in dosage.

**APPLICATION TO OTHER TISSUES**

The application of radioiodine treatment in breast cancer remains a possibility, due to endogenous NIS expression within breast tumours. Although the signalling pathways that drive NIS expression are different to those in thyroid cancer and, for example, MEK inhibitors are not useful, the effects of the NIS interactors PBF, ARF4 and VCP on radioiodine uptake are consistent in breast cancer and may represent effective targets for enhancing the functionality of NIS within these tumours.

Finally, progress continues to be made in the targeted delivery of the NIS gene to multiple tumour types, including hepatocellular carcinoma and colon cancer, in order to facilitate radioiodine treatment. Modulation of these NIS interactors may therefore boost the efficacy of exogenous NIS delivery in multiple other tumours. Overall, the stimulation of radioiodine uptake via NIS has great clinical potential which continues to gather momentum.

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VICKI SMITH

Lecturer in Molecular Endocrinology, University of Birmingham
The British Thyroid Foundation (BTF) was launched in Harrogate at the 11th Joint Meeting of the British Endocrine Societies (the forerunner of the Society for Endocrinology BES conferences), back in March 1992. This November, the SfE BES conference will return to this Yorkshire town, as the BTF marks a quarter of a century of providing thyroid patients with reliable information and support to help them manage their diagnoses.

Over the years, the BTF has developed close partnerships with medical professionals to ensure that not only do patients receive information of the highest standard, but that the patient perspective is fed back to the clinicians who make the decisions that affect and improve patient care.

Patients access BTF support through a comprehensive range of patient literature, regional support groups, a network of volunteer telephone contacts, newsletters, patient films, information events and Facebook groups. The information is freely accessible to them (and medical professionals) on the BTF website (www.btf-thyroid.org), and hard copies of leaflets are sent out to hospitals and clinics who request them.

The BTF is also committed to supporting research, and each year presents the BTF Research Award of up to £20,000 for work in the thyroid field.

CURRENT INITIATIVES

The charity always welcomes feedback and suggestions from patients, and their views and experiences often form the basis of new activities. We have a range of current projects.

The Hypothyroidism Care Strategy focuses particularly on communicating key messages to GPs.

The Thyroid Eye Disease (TED) Project seeks to improve understanding, treatment and care for patients with TED (see page 6 for details of our work with TEAMeD).

Members of the Thyroid Cancer Project have recently worked together to make submissions to the Welsh, Scottish and English organisations that appraise new medicines for the treatment of advanced thyroid cancer. This year they have also published a third edition of their popular booklet Thyroid Cancer: For Patients, By Patients (see page 27 for further information).

The Children’s Project has also had a busy year. In May we hosted a second Children’s Conference which brought families together from across the UK. The event, in Westminster, gave parents and their children the opportunity to listen to leading medical experts, share their concerns and stories, and hear about the experiences of others. On the right of this page, you can read the words of Joe Straw, a young adult with congenital hypothyroidism who spoke at the conference.

Although much has been done to improve understanding of thyroid disorders over the last 25 years, not least to increase the availability of patient friendly information, the BTF still has a valuable role as a link between patients and the medical profession. Patient concerns haven’t changed and many people need somewhere to turn to after diagnosis. The BTF is an important and reliable resource that we hope will be here for years to come.

JOE’S STORY

One of the speakers at this year’s Children’s Conference was Joe Straw, an inspirational 22-year-old from Sheffield, who spoke about the sometimes painful journey he’d had growing up with congenital hypothyroidism (CH):

‘I was diagnosed with CH at birth. It was a very anxious time for my parents and close family, and they recall the lack of information that was available to them. However, my hypothyroidism was generally well controlled throughout my childhood. My parents made sure I took my levothyroxine each morning before breakfast and I was able to do the things I enjoyed, just like everybody else my age, and I progressed well at school.

‘When I was about 15 years old I was placed under the care of a GP and, unfortunately, the good care that I had received ended abruptly. I began feeling very unpleasant physical, psychological and emotional symptoms in my final year of school, including severe headaches, lethargy and anxiety. I stopped playing football and became very disinterested in life. Ultimately I failed my GCSEs and left school with no qualifications. Despite this, my GP failed to recognise that my now uncontrolled thyroid was the cause.

‘By 16 I was anxious, apathetic and depressed. I couldn’t hold down a job and my self-esteem hit rock bottom. At 17, I was prescribed antidepressants and the symptoms I’d experienced for such a long time progressed further. My behaviour became reckless and self-destructive and for 2–3 years I self-medicated in an effort to forget my symptoms and the feelings I had.

‘I requested a change of GP and this proved to be pivotal. Blood tests revealed that my T4 was nearly undetectable and my TSH had reached 100mU/L. I was referred urgently to Professor Tony Weetman at the Royal Hallamshire Hospital in Sheffield. He asserted, in no uncertain terms, that we must take immediate action to avoid potentially serious long term effects. My dose of levothyroxine was reduced and I made sure I took it properly. After another blood test, my dose was increased slightly and I am delighted to say that I have been well ever since. The symptoms that had plagued me for 3 years are long gone and my TSH/T4 have been consistent for 4 years.

‘Having got my life back, I retook my exams and progressed to university to study. Alongside my studies and work I have been able to play sport again, even competing in boxing for 4 years! I live a very active life once again, and can now make up for lost time. I volunteer for the BTF and really value the opportunity to share my experiences of living with thyroid disease as a way of helping others.’

JULIA PRIESTLEY

Development Officer, British Thyroid Foundation
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WHY IS RESEARCH IMPORTANT IN THE ‘POST-TRUTH’ ERA?
FROM OUR SCIENCE COMMITTEE CORRESPONDENT

Ignorance and stupidity are answers that slip off the lips. However, it is easy to forget that while we are all experts in our own little patch of intellectual or technical real-estate, we all have ‘faith’ and believe in a multitude of things that we understand little about every single day.

How many of us truly understand how the brakes in our car work, or what keeps planes in the air? Yet we all drive or fly, and (most of us anyway) believe that humans have and continue to play a major role in global warming. We trust that other experts are doing their job (as we are doing ours) and getting things right and, as a result, society functions.

The problem is, how does one tell an actual expert from a fake in this ‘post-truth’ era? If you are of an orange hue and tweet nonsense in the early hours, many people will believe you because surely, as the ‘leader of the free world’, you will have access to the relevant information? If you are a ‘doctor’ claiming that vaccines cause autism, surely you know what you are talking about?

The only way to combat this degradation of the value of truth is to be, as scientists, passionate about the truth. We have to find out the truth, tell the truth and call out untruths whenever and wherever we can.

GILES YEO
Science Committee correspondent
Twitter: @GilesYeo

A ‘lifestyle’ website, which shares the first three letters of its name with a certain internet search engine and is fronted by a recently ‘consciously uncoupled’ actress, has, just this year, felt the need to speak out on ‘The mysteries of the thyroid’.

The expert voice they rely on is a self-proclaimed ‘medical medium’ who (and I quote) ‘can scan the body from afar, and with the help of “Spirit” explain what ails or does not’. Perhaps this, at long last, explains how the trusty medical tricorder of Star Trek’s Dr ‘Bones’ McCoy actually works!

Millions of people visit this particular website to buy lifestyle items (jade eggs for your ‘yoni’ anyone?) and obtain health ‘advice’. Yet, while this may be one high-profile example, the darker recesses of the internet are populated with many other such sites.

The astrophysicist Neil deGrasse Tyson famously said about science, ‘It’s true whether or not you believe in it. That’s why it works.’ Why, then, do so many people believe what clearly are, at least to us scientists, alternative facts?

SPECIALISED ENDOCRINOLOGY CRG: LATEST DEVELOPMENTS
FROM OUR CLINICAL COMMITTEE CORRESPONDENT

The Specialised Endocrinology Clinical Reference Group (CRG) continues to strive for our discipline through NHS England.

Further to my last update in The Endocrinologist (issue 123, page 9), we have now introduced pegvisomant up and down the country, and this should be accessible through Blueteq. This means that everybody who fulfils the agreed criteria (which have been publicised and can be found at http://bit.ly/2vcbwPL) can access pegvisomant. If there are problems, please let us know.

Pasireotide for the treatment of Cushing’s is also coming through Blueteq.

‘We are about to revise the national service specification, with a view to delineating the conditions to be treated as ‘specialised’ … If you have views on this issue, please let us know.’

I think everybody should now be aware of the endocrine dashboard. Hopefully endocrinologists are setting up links with their performance and contracts teams and together are filling it in, so that we can obtain useful data. While it is not perfect, it does assess some aspects of endocrine care, and this will hopefully enable us to make comparisons across the country.

We are in the process of ensuring good quality care for patients with adrenal cancer and neuroendocrine tumours by ensuring the presence of multidisciplinary teams and effective networks. Neuroendocrine tumours are, for the most part, managed in European Neuroendocrine Tumor Society (ENETS)-accredited centres in most parts of the country.

We are about to revise the national service specification for specialised endocrinology, with a view to delineating the conditions to be treated under NHS England as ‘specialised’. We will be defining criteria for inclusion and exclusion during this reiteration. If you have views on this issue, please let us know.

We intend to arrange a meeting to discuss commissioning in endocrinology at the forthcoming Society for Endocrinology BES conference on Wednesday 8 November. We look forward to seeing you there if you would like to discuss any of these matters further, though you are of course very welcome to contact us in the meantime.

JOHN WASS
Professor of Endocrinology, University of Oxford
Chair, Specialised Endocrinology Clinical Reference Group

You can find more information on the work of the Group at http://bit.ly/2vbMWhY.
Securing the Society’s future: 
A DISCIPLINE THAT THRIVES

WRITTEN BY GRAHAM WILLIAMS, IAN RUSSELL & LAURA UDAKIS

Our Society exists to support a vibrant community of professionals working within endocrinology in the UK and beyond. We want endocrinology as a discipline to thrive, its importance to be recognised and for it to be applied to tackle global challenges.

As with any organisation, it’s important that we take stock every few years to ensure our activities are working as hard as they can to achieve our vision.

The Society is currently going through this process, working with Council, committees and the wider membership to identify a strategic framework to focus our work for the next 4 years (2018–2022). This will help us effectively channel our precious time and energy and invest in initiatives that will add maximum value to strengthen the Society.

OUR STRATEGIC FRAMEWORK

We continue our pursuit of three major goals for the Society:

Further our fundamental understanding of endocrinology
Use the latest thinking in endocrinology to improve patient care
Engage non-specialists with the impact and potential of endocrinology

Our work can be categorised within five focus areas that will allow us to meet these major goals:

Recruiting the next generation
Supporting career development at all stages
Setting the highest standards
Providing platforms for knowledge exchange
Collaborating within and beyond the endocrinology community

IDENTIFYING THE PRIORITIES

Our recent membership survey gave you the opportunity to have your say about the future priorities for the Society. The strongest message was to make more efforts to attract non-specialised students into endocrinology to secure the future of the discipline. Other areas you told us were particularly important were investing in clinical guidance and research, and promoting endocrinology in the mainstream media.

It is also clear that the Society must work extra hard to ensure it is relevant to all the professionals we represent—scientists, clinicians and nurses—both within endocrinology and also working in roles relevant to endocrinology.

MOVING FORWARD

Our job now is to identify the priorities, targets and key measures within these areas, over which our Council and committees will take ownership. Underpinning this work are also several principles that we won’t lose sight of in our work:

• Providing valuable, accessible member benefits
• Growing the diversity of the membership
• Ensuring we are a stable, resilient, efficient and diverse organisation.

Some of the priorities that have been identified to improve the way that you, our members, interact with the Society include putting more member services online and facilitating online member-to-member communications to make it easier for you to engage with the Society and work with one another. We will also get better at targeting Society information so that you receive the most relevant updates and opportunities through the right channels.

If you want to say more about what you think the Society should be focusing on over the next 4 years, please do get in touch at ian.russell@endocrinology.org.

GRAHAM WILLIAMS Society President
IAN RUSSELL Chief Executive
LAURA UDAKIS Director of Membership Engagement
Society News

SfE BES 2017
HARROGATE CALLING

The Society for Endocrinology BES Conference 2017 is just around the corner on 6-8 November. We have a bustling programme of scientific and clinical sessions, workshops and debates for you to look forward to this year.

Harrogate Highlights

Meet the Expert Sessions
Head on over to one of the many ‘Meet the expert’ sessions, where you will find updates on diverse subjects, such as next generation sequencing, hormone replacement and management of hyperthyroidism in pregnancy:

What can next generation sequencing do for you? In the clinic and the lab
Cecilia Lindren (Oxford, UK)

Growth hormone replacement across the ages
Stephanie Baldeweg (London, UK)

Highlighting management of hyperthyroidism in pregnancy
Stine L. Andersen & Kristien Boelaert (Aalborg, Denmark & Birmingham, UK)

Fascinating Lectures
Exciting lectures at this year’s conference include talks by national and international plenary medallists, which will appeal to delegates with either a scientific or a clinical focus:

Next generation tools to understand endocrine function in health and disease
David Hodson (Birmingham, UK)

Corticosteroids and the brain
Marian Joëls (Utrecht, The Netherlands)

Primary hyperparathyroidism: molecular genetic insights and clinical implications
Andrew Arnold (Farmington, CT, USA)

Join the Debate
The 2017 debate is a must-see event, as Roy Taylor and Abd Tahrani discuss the growing issue of obesity, and whether food taxation is the right tool with which to tackle it:

This house believes that the UK population trend in obesity cannot be reversed without food taxation

FOR Roy Taylor (Newcastle upon Tyne, UK)

AGAINST Abd Tahrani (Birmingham, UK)

Nurses’ Sessions
Events for endocrine nurses at this year’s conference provide a comprehensive overview of two complex endocrine conditions, importantly including the patients’ perspective of living with these diseases:

Cushing’s disease/syndrome – the facts and hot topics

Diabetes insipidus

Register now and view the entire scientific programme by visiting: www.endocrinology.org/events/sfebes2017

Stay up to date with everything at #SFEBES17
THE 2017 SOCIETY FOR ENDOCRINOLOGY BES CONFERENCE IS JUST AROUND THE CORNER. HERE, PROGRAMME SECRETARY SIMON PEARCE PROVIDES AN INTRODUCTION TO THE CONFERENCE AND THREE ATTENDEES TELL US WHAT THEY ARE LOOKING FORWARD TO MOST.

VIEW FROM THE PROGRAMME SECRETARY SIMON PEARCE

For the Society for Endocrinology BES 2017 conference in Harrogate, I am looking forward to a very strong programme on several subjects including calcium and bone, thyroid, and female reproductive endocrinology.

Following the success of last year’s thyroid masterclass, we have scheduled a bone masterclass with two internationally respected experts on osteoporosis, a clinical management symposium on hyper- and hypo-calcemia and a session on steroids and bone. Meet the expert sessions on opiates-induced hypopituitarism, hyperthyroidism in pregnancy and next-generation DNA sequencing promise to keep me up to date on the latest advances in these important and fast-moving areas.

We also welcome more than 20 overseas speakers, including cutting edge plenary lectures from some giants in our field, Teresa Woodruff, Andrew Arnold and Martin Schlumberger. Home-grown highlights will also include two well-known members of our Society, Andrew Hattersley and Julia Buckingham, who never fail to both entertain and inform.

Looking forward to seeing you in Harrogate!

A SCIENTIFIC PERSPECTIVE

TONY COLL

Fat Rascals, Yorkshire Tea and windy walks across ‘The Stray’ are back; after a sojourn on the south coast, SIE BES 2017 returns to Harrogate, a venue familiar to many. However, although the framing is familiar, this year’s programme is bursting with new directions and reinvigorating topics.

The old world charms of this comfortable spa town don’t immediately conjure up the rather more scruffy rascals of Renton, Begbie and Spud but, with a session on the endocrinopathy of ‘Trainspotting’, perhaps we can view their behaviour in a more sympathetic light. Further evidence too for the case of hormones being behind all the best stories in a day job continually throws up new clinical issues and the top tips from the ‘How do I’ sessions are always helpful. The bone metabolism ‘Meet the Expert’ session also looks good as does the Clinical Management Workshop on calcium.

Some of the emerging themes we’ve touched on in the pages of The Endocrinologist are covered – the collateral damage of cancer, how to engage in the media, steroids and the skeleton – but now you’ll have the chance to discuss these topics with experts in their field.

I will also be looking out for the Applied Physiology Workshop on tissue engineering, wondering how close we are to switching from hormone replacement therapy to whole organ regeneration.

Finally, there is a tantalising plenary lecture – ‘What to watch: three breakthroughs that may change our lives in the next 10 years’. What are they going to be? Dunno – better go and have a look.

CLINICAL CONSIDERATIONS

HELEN SIMPSON

Admittedly I’m biased but this programme looks exciting. As always, the plenary lectures are a highlight – world-class endocrinologists sharing their wisdom. It will be particularly nice to hear two of my old home team speak, Professors Savage and Vidal-Puig.

The day job continually throws up new clinical issues and the top tips from the ‘How do I’ sessions are always helpful. The bone metabolism ‘Meet the Expert’ session also looks good as does the Clinical Management Workshop on calcium.

There are the usual program clashes – symposia on succinate dehydrogenase or pituitary disease in adolescents? I think I’ll dart between the two. I’m going to sneak into the Senior Endocrinologists’ session (clearly far too young to qualify just yet) to hear Professor Shalet speak about cancer survivors. I need ideas on how to best manage the services we offer as patient numbers increase rapidly.

Apart from science, meeting old friends, sparking new ideas, and support from endocrine friends as we go through different career stages is always a bonus. It’s going to be a busy 3 days…

EARLY CAREER OUTLOOK

NYO NYO TUN

This year’s programme has some choice topics backed up with fantastic speakers. The plenary lectures will be a must and I look forward to the topical debate on obesity and food taxation on Monday.

Choose ‘Meet the Expert’ sessions for some thought-provoking talks and choose Clinical Management Workshops to refine your clinical practice. I certainly will!

There are also a variety of talks tailored just for our early career members including ‘Skills: How to engage with media’, the Future sessions, and our flagship Early Career Symposium ‘Where will endocrinology take you’.

The Early Career dinner and quiz will also be a must. It’s already a win to catch up with people and meet new members, but it’ll be a bonus to answer some questions … correctly. I’ll also be looking forward to seeing another dance off this year!
The Society makes several awards at the Society for Endocrinology BES conference. Here, we recognise the talent of endocrinologists at all career stages.

<table>
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<tr>
<th>MEDAL LECTURERS 2017</th>
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<tr>
<td><strong>Dale Medal</strong></td>
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<tr>
<td>Andrew Hattersley (Exeter)</td>
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<td>Diagnostic diabetes: a paradigm shift</td>
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<td><strong>Jubilee Medal</strong></td>
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<td>Julia Buckingham (London)</td>
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<td>Bacteria, steroids and formyl peptide receptors – more twists to the inflammatory response</td>
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<td><strong>Transatlantic Medal</strong></td>
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<td>Teresa Woodruff (Chicago, IL, USA)</td>
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<td>What to watch: three breakthroughs that may change our lives in the next 10 years</td>
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<td><strong>International Medal</strong></td>
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<td>Andrew Arnold (Farmington, CT, USA)</td>
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<td>Primary hyperparathyroidism: molecular genetic insights and clinical implications</td>
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<td><strong>European Medal</strong></td>
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<td>Marian Joëls (Utrecht, The Netherlands)</td>
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<td>Corticosteroids and the brain</td>
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<td><strong>Society Medal</strong></td>
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<tr>
<td>Toni Vidal Puig (Cambridge)</td>
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<td>Adipose tissue expandability, lipotoxicity and the metabolic syndrome</td>
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<td><strong>Starling Medal</strong></td>
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<td>David Hodson (Birmingham)</td>
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<td>Next generation tools to understand endocrine function in health and disease</td>
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<th>JOURNAL AWARD WINNERS 2017</th>
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<tr>
<td><strong>Journal of Endocrinology</strong></td>
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<tr>
<td>Iulia Potorac et al. (Liège, Belgium)</td>
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<td>A vital region for human glycoprotein hormone trafficking revealed by an LHB mutation (doi:10.1530/JOE-16-0384)</td>
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<td><strong>Journal of Molecular Endocrinology</strong></td>
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<td>Kristine Wadosky et al. (Chapel Hill, NC, USA)</td>
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<td>MuRF1 mono-ubiquitinates TRα to inhibit T3-induced cardiac hypertrophy in vivo (doi:10.1530/JME-15-0283)</td>
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<td><strong>Endocrine-Related Cancer</strong></td>
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<td>Allison Sumis et al. (Washington, DC, USA)</td>
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<td>Social isolation induces autophagy in the mouse mammary gland: link to increased mammary cancer risk (doi:10.1530/ERC-16-0359)</td>
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<tr>
<td><strong>Endocrine Connections</strong></td>
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<tr>
<td>Ashley Reeb et al. (St Louis, MO, USA)</td>
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<td>Characterization of human follicular thyroid cancer cell lines in preclinical mouse models (doi:10.1530/EC-15-0114)</td>
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<tr>
<td><strong>Clinical Endocrinology</strong></td>
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<td>Sathikathala Narayanaswamy et al. (London)</td>
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<td>Subcutaneous infusion of kispeptin-54 stimulates gonadotrophin release in women and the response correlates with basal oestradiol levels (doi:10.1111/cen.12977)</td>
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<th>EARLY CAREER PRIZE LECTURERS 2017</th>
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<tr>
<td><strong>Science lecturer</strong></td>
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<tr>
<td>Caroline Gorvin (Oxford)</td>
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<td>Insights into GPCR trafficking and biased signalling by studies of centrexin homestead</td>
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<tr>
<td><strong>Clinical lecturer</strong></td>
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<tr>
<td>Jackie Maybin (Edinburgh)</td>
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<tr>
<td>The role of hypoxia in the physiology and pathology of menstruation</td>
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**SOCIETY NEWS**

Winning awards:

**IN RECOGNITION OF EXCELLENCE**

Make your work reach further

Flexible grants up to €2,000 available for early career scientists and clinicians to support networking and collaborative research.

Find out more and apply at [www.bioscientificatrust.org](http://www.bioscientificatrust.org)
Endocrine Networks
LAUNCH DEDICATED WEBPAGES

The Society’s Endocrine Networks were created as platforms to enable basic and clinical researchers, clinical endocrinologists and endocrine nurses to share knowledge and best practice and work together to advance their specialist field.

Now, keeping informed on your Network’s activities has never been easier. The new Endocrine Network webpages are designed to keep you updated with the latest news from the Networks, as well as any related events and opportunities. As a Network member, you can also access a repository of relevant information sources, patient support groups and training opportunities. Get involved and share your own resources to help to make these pages an even more valuable tool for the Network.

Find them all at www.endocrinology.org/membership/endocrine-networks.

Not yet a member of a Network? Becoming one is easy – just log into the Members’ Area on our website and select ‘Endocrine Networks’.

Endocrine ACADEMY

Clinical UPDATE
16-18 April 2018
Endocrine NURSE UPDATE
16-17 April 2018
Career DEVELOPMENT WORKSHOPS
16-18 April 2018

Hilton Birmingham Metropole
NEC, BIRMINGHAM, UK

SAVE THE DATE

www.endocrinology.org/events
SfE members received the gift of free publishing* in Endocrine Connections this year – the Society’s open-access endocrinology journal.

We spoke to Society member Lawrence Hayes from the University of Cumbria regarding his recent free publication in Endocrine Connections entitled ‘Exercise training improves free testosterone in lifelong sedentary aging men’. Endocrine Connections 2017 6 306–310 doi:10.1530/EC-17-0082.

“We conducted this study because previous investigations have displayed considerable ambiguity around the effect of exercise on testosterone.

“A group of lifelong sedentary ageing men were given a regime of aerobic exercise in line with the public health guidelines of 150 minutes per week. The participants were then moved to a regime of low frequency–high intensity interval training. Total and free testosterone were measured before and after each change in exercise regime.

‘The results of our study showed that total testosterone was increased by just doing the minimum physical activity recommended by the guidelines.

What was surprising was that when we reduced exercise training volume to high intensity interval training once every 5 days, total testosterone was maintained at a higher level, sex hormone binding globulin did not increase and overall free testosterone was increased. Free testosterone is not bound to a carrier protein in the blood, enabling it to get into tissue such as fat and muscle and exert its effect. This is important because we know from cross sectional studies that testosterone is positively correlated with body composition and physical and mental wellbeing.

‘Our future work is going to determine if this phenomenon is also present with masters athletes – those who have been exercising their entire life.’

This work was published for free* in the Society’s open-access journal Endocrine Connections.

Endocrine Connections has recently received its first impact factor of 2.541, so now is a great time to submit your research. Submit now at www.endocrineconnections.com.

*(Terms & Conditions apply).

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*(Terms & Conditions apply).

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

WHAT DOES AN ENDOCRINE AMBASSADOR DO?
As an Endocrine Ambassador, you’ll be your institution’s champion for endocrinology, bringing the many different flavours of our discipline together, and you’ll encourage students and colleagues to join the Society for Endocrinology.

As part of this role, you’ll be expected to:

- organise small research seminars in your organisation to bring students and colleagues together around a relevant interdisciplinary theme; to do this, you can apply for the Endocrine Ambassador Grant of £100 (£200 in exceptional circumstances)
- promote the Society for Endocrinology by displaying printed materials about the Society within your institution, and informing your colleagues and students about the benefits of membership
- act as a proposer for new Society membership applications from your institution.

Each year, the three Endocrine Ambassadors who have recruited the most new members will receive free annual membership to the Society for Endocrinology.

FUNDING SUPPORT
A maximum of 20 grants, each of £100 (£200 in exceptional circumstances), are available to Endocrine Ambassadors on a first come, first served basis to support a small event aimed at encouraging interdisciplinary collaboration and recruiting new members to the Society. The funding will be either to provide refreshments or to provide support for a speaker.

BECOME AN ENDOCRINE AMBASSADOR
To apply to become an Endocrine Ambassador, head to www.endocrinology.org/membership/endocrine-ambassadors.

For its 2017 intake of Ambassadors, the Society is aiming to recruit scientists from its ‘Full’ and ‘In-Training’ membership categories.
Endocrinology is one of the older scientific pursuits, imbuing it with an undeserved veneer of research stagnation: surely all major endocrine findings have been made, haven’t they?

However, this could not be further from the truth, as our recent Society for Endocrinology Themed Scientific Meeting highlighted. Here, we explored how sulfation and desulfation – fundamental, evolutionary conserved pathways – regulate and control steroid hormone action.

BACKGROUND
Steroid hormones circulate mainly in their sulfated form, in particular oestrogens and dehydroepiandrosterone (DHEA). They require desulfation by steroid sulfatase to become active. Conversely, many hormones can be sulfated by sulfotransferases, making them in general inactive, with increased water solubility to expedite transport in the blood and subsequent excretion. Traditionally, sulfation was held to act purely as a means by which hormones were removed from the circulation.

However, with our greater understanding of intracrine metabolism, evidence now suggests that sulfation/desulfation pathways play a major role in regulating steroid action locally. Targeting this local formation of active hormones may prove fruitful for the treatment of numerous diseases, including metabolic disease, endometriosis and steroid-dependent cancers.

Furthermore, due to recent technological advances, particularly in the field of mass spectrometry, our abilities to measure sulfated and non-sulfated hormones have become much more sensitive. Thus, there is considerable interest in utilising these new methods to fully appreciate how active hormone concentrations are regulated at the cellular level.

SPRINGBOARD TO SUCCESS
Our recent comprehensive review on steroid sulfation and desulfation1 turned out to be a springboard from which to build our growing appreciation of sulfation biology. The next logical way forward was to organise a meeting primarily focused on identifying potential pathways within sulfation and desulfation that are ripe for targeting to treat disease.

Receiving a much sought-after Society for Endocrinology Themed Scientific Meeting Grant enabled us to bring together the world leaders in sulfation and desulfation at the University of Birmingham. The application process was very straightforward and allowed for flexibility regarding the timing of our meeting.

Furthermore, on the back of this grant, we were able to secure further funds through an MRC Proximity to Discovery Grant, designed to facilitate key interactions with industry leaders. Subsequently, we had representatives at the meeting from a range of partners, which allowed interaction between academia and industry, leading to potential future collaborations.

BREADTH AND DIVERSITY
The event we organised involved many world-leading researchers, challenging numerous aspects of sulfation and desulfation research. Despite having a rather specific title, our meeting actually encompassed a rather broad scope, providing many talking points, which augmented collaboration throughout the conference.

‘Very few professional scientific societies offer such a significant amount of money (up to £10,000) with which to organise a scientific meeting.’

Talks covered such diverse topics as targeting steroid desulfation in breast cancer, measuring disulfates by mass spectrometry, sulfated androgens in women’s health, and even hormone sulfates in the porcine testicular compartment! A number of novel ideas focused on targeting desulfation were also explored, highlighting the translational potential to treat disease that is inherent in these pathways.

In summary, we were extremely happy with how the Society for Endocrinology Themed Scientific Meeting Grant helped us organise this conference. Very few professional scientific societies offer such a significant amount of money (up to £10,000) with which to organise a scientific meeting. Bolstered by this good experience, we will be looking forward to (organising) further meetings focused on sulfation and desulfation pathways in the future.

PAUL A FOSTER & JONATHAN WOLF MUELLER
Institute of Metabolism and Systems Research, University of Birmingham

REFERENCE
The Society for Endocrinology operates a Corporate Supporters’ scheme to strengthen our relationship with industry and further our charitable objectives.

We are delighted to highlight the activities of some of our Corporate Supporters here. We thank them for their support and contribution to scientific and clinical endocrinology. Corporate support is vital to the Society for Endocrinology, enabling us to further our charitable objectives and engage with endocrinologists, supporting their learning and advancing the science of endocrinology.

For further information, visit [www.endocrinology.org/corporate](http://www.endocrinology.org/corporate) or contact amanda.helm@endocrinology.org.

**Pfizer** is one of the world’s premier innovative biopharmaceutical companies, discovering, developing and providing over 100 different medicines, vaccines and consumer healthcare products that help save and transform the lives of millions of people in the UK and around the world every year.

For more than 25 years, Pfizer Endocrine Care has been committed to the advancement of endocrinology. This is demonstrated by our innovations in endocrine care: Pfizer UK was the first company to launch single-dose and multi-dose growth hormone (GH) delivery devices; it has built up the largest international databases of patients receiving GH therapy; and it produces the first and only GH receptor antagonist for the treatment of acromegaly.

The Society for Endocrinology has agreed a 2-year partnership with Pfizer. The agreement is the first of its kind for the Society, and aims to deliver maximum benefit to both organisations and the broader aim of advancing endocrinology.

Paul Carroll, Chair of the Society for Endocrinology Corporate Liaison Board, says

“The partnership recognises the Society for Endocrinology’s commitment to working with industry to achieve its objectives. It represents a true collaboration with an industry partner, working on joint projects for the benefit of endocrinology.”

James Steed, UK Lead for Endocrine Care at Pfizer, comments

“The NHS is changing in response to various pressures, and the needs of our partners and the people they care for reflect this. We believe that, through working in partnership, combining our skills, experience and resources, together we can tackle some of the greatest challenges facing the NHS today. The new partnership will strengthen Pfizer’s relationship with the Society, and ultimately improve patient care.”

To find out more about what Pfizer are doing to support the NHS and patients in the UK, please contact Endocrine Country Brand Lead on +44 (0)1304 616161.

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Tel: +44 (0)1304 616161
Web: [www.pfizer.co.uk](http://www.pfizer.co.uk)
Bioscientifica exists to support biomedical communities. Through our expertise in publishing, events and association management, we work to strengthen societies to advance science and health. Bioscientifica is wholly owned by the Society for Endocrinology, and we apply this firsthand knowledge to help the societies we work with to overcome challenges and advance their disciplines.

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Web: www.bioscientifica.com

Shire is the leading global biotechnology company focused on serving people with rare diseases and other highly specialised conditions. We strive to develop best-in-class products, many of which are available in more than 100 countries, across core therapeutic areas including haematology, immunology, neuroscience, ophthalmics, lysosomal storage disorders, gastrointestinal/internal medicine/endocrine and hereditary angioedema; and a growing franchise in oncology.

Our employees come to work every day with a shared mission: to develop and deliver breakthrough therapies for the hundreds of millions of people in the world affected by rare diseases and other high-need conditions, and who lack effective therapies to live their lives to the fullest.

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Tel: +44(0)1256 894003
Web: www.shirepharmaceuticals.co.uk
OPPORTUNITIES TO LEARN
MAKING THE MOST OF
NEVER SAY NO:
WRITTEN BY MARIA RAVELO

‘How about you visit us and we can show you around?’ I remember those few words very well, and I will always be grateful for them.

First, I should take you back 3 years, to my very first month as an endocrine specialist nurse. I was told that it was a fairly new post, covering two district general hospitals, and that I would be working closely with the consultants to help develop the role. Having worked in the emergency department, I was no stranger to pressure, but I found it to be more challenging having to work autonomously, with no other endocrine nurse present within the Trust to turn to for support. I remember reflecting, ‘I can’t help but think that this one will be impossible to pull off.’

THE POWER OF NETWORKING
During my first few weeks, I came across a TV documentary programme about a young girl with an endocrine disorder. In one of the scenes, I spotted an endocrine nurse performing a venipuncture, and noted his details. The next morning, I contacted clinical nurse specialist Sherwin Criseno from the Queen Elizabeth Hospital (QEH), Birmingham. From that moment, the networking doors opened for me! I was able to attend my first conference, learned more about the Society for Endocrinology and created important links at the same time. It was an eye opener, as I suddenly realised it wasn’t going to be a lonely world after all.

As the days went by, my work demands increased and everything suddenly became very hectic. At the same time, I was also aware that I needed to explore and develop my role further.

GAINING EXPERIENCE
My wise consultant mentor once said, ‘It’s all about balance!’ and, soon afterwards, I had the chance to arrange work experience at a tertiary hospital in London. This was my first period of work experience and was not as straightforward as I had expected. There were a few challenges, including preparation, staffing issues and travelling. Work experience clearances alone took over 2 months to complete!

I undertook a total of 3 days over the course of 3 weeks, and all this time was spent in the investigations unit. The hospital’s staffing levels were at their tightest during the time of my visit, which was unfortunate. However, over a short period, I was able to observe how they organised, prepared and performed some of their dynamic function tests, including those with which I wasn’t familiar. My learning objectives were not clear at that time, but I was like a sponge ready to absorb anything that I observed. I found it mentally exhausting, but equally positive.

TAKE EVERY OPPORTUNITY
As the years progressed and my workload increased, I realised that I was so focused on my daily activities that I was beginning to de-prioritise my own learning needs. It was around March 2017 when I contacted my colleagues at QEH for a catch-up conversation. Little did I realise that a simple phone call would, yet again, open the door to another fantastic opportunity for me.

It was on this occasion that I was asked, ‘How about you visit us and we can show you around?’ What had started as a brief chat turned into a work experience reality.

Unlike my first period of work experience, this time I had clear objectives regarding what I needed and wanted to learn. I particularly wanted to observe nurse-led clinics, including those for thyroid, rare disorders and bone. True to my colleague’s words, within a week I had received my work experience schedule, matched to my learning needs. I was impressed by how quickly they made the arrangements, and their dedication to supporting a colleague.

I couldn’t contain my excitement and, indeed, I was not disappointed. On the first day, I was immediately introduced to the team and had a tour of the department. My timetable for the 3 days of work experience was followed through, with plenty of room to adjust it as necessary. I could switch to different clinics of interest, and every person on the team made me feel welcome.

We went through different pathways, protocols and procedures, which I found very useful. Although there were some differences in terms of practice (e.g. growth hormone pathways and funding), it was helpful to witness how another centre operated and how they provided safe and efficient delivery of care to their service users.

LEARN ON YOUR FEET
I’m sure you will agree that there are many ways to learn and improve one’s knowledge and skills. There are various competency packages, courses and academic pathways to explore. However, with rising demands in our profession and constant changes in practice, I believe that work experience plays an important role in our professional development. It is a flexible, effective and robust learning tool, which you could embark upon within your local practice or extend on a wider scale.

I can think of many words to describe my work experience opportunities, and I can’t stress strongly enough how highly rewarding, diverse, exciting and challenging they truly were. They certainly exceeded my expectations, gave me a different perspective and added great understanding to help enhance my current and future practice.

MARIA RAVELO
Endocrine Specialist Nurse, East Sussex Healthcare NHS Trust
The autumn issue of *The Endocrinologist* always reminds me that the Society for Endocrinology BES conference is just around the corner. This is always a great opportunity to meet up with colleagues and friends, old and new. It also encompasses all that networking is about: sharing knowledge, experience and ideas to improve clinical practice and thereby enhance patient care.

Maria Ravelo’s article on the previous page describes her journey since being appointed as an endocrine specialist nurse. Her pathway into endocrine nursing probably sounds familiar to most endocrine nurses. It can seem daunting in the beginning, often working alone and appointed to develop a new nursing service. However, Maria demonstrates that there is always help out there, as she shares with us a great example of the benefits of networking. Her visits to other endocrine centres enhanced her learning and knowledge through such experience. The Society for Endocrinology Competency Framework for Adult Endocrine Nursing\(^1\) can complement such learning, allowing nurses to identify where they currently fit in practice, and their learning needs and aims for the future.

Patient care also is enriched through research and audit, and I am excited to announce the introduction of the Society for Endocrinology Endocrine Nurse Grant. This is an exciting opportunity not only to build upon evidence-based care, but also to develop nurses’ professional profiles. Further details of the grant can be found on this page.

If you have an idea for future articles in *The Endocrinologist* or programme suggestions please do not hesitate to get in touch. Alternatively, you can meet and talk further with members of the Nurse Committee at SfE BES 2017 in November. I look forward to seeing you there!

**BEST WISHES**

LISA SHEPHERD

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The Society for Endocrinology is delighted to announce the launch of a new grant for its Nurse Members.

The new Endocrine Nurse Grant will support nurses who seek funding for a research or audit project to enhance nursing/clinical practice, or those who wish to produce preliminary data as part of a full application for a competitive doctoral research fellowship at the start of a PhD programme.

There will be two deadlines per year: 27 May and 27 November, commencing November 2017. Up to £5,000 will be available at each deadline.


Developed by the Society’s Nurse Committee, this grant will enhance the profile of those within the nursing profession, and will provide an additional member benefit by extending the Society’s grants portfolio.

The launch of this grant provides an excellent opportunity for nurses working in endocrinology to undertake a piece of research or audit. This will fundamentally not only improve practice and positively impact upon patient care, but enhance the nurses’ professional profile.

Lisa Shepherd, Chair, Nurse Committee

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NEW BTF THYROID CANCER BOOKLET

The third edition of the British Thyroid Foundation (BTF)’s valuable and successful thyroid cancer booklet is now available. Designed to help patients facing a diagnosis of thyroid cancer, the booklet *Thyroid Cancer: For Patients, By Patients* is largely written and reviewed by patients who’ve experienced a diagnosis of thyroid cancer.

It is endorsed by the British Thyroid Association (BTA), British Association of Endocrine and Thyroid Surgeons, Association of Multiple Endocrine Neoplasia Disorders (AMEND), Butterfly Thyroid Cancer Trust, Thyroid Cancer Support Group Wales, Hypopara UK and the Caledonian Society for Endocrinology and Diabetes.

“The BTA is delighted to endorse the updated BTF patient support booklet for thyroid cancer. It is evident that there is a great demand for clear and accessible information for patients with thyroid cancer, on what can be a complex pathway through many specialties. As health professionals, it is our duty to provide consistency to patients and their families. This booklet provides the recommended highest quality standards and support that health professionals should be delivering to their patients with thyroid cancer.”

Mark Vanderpump, BTA President

“A superb comprehensive go-to resource for thyroid cancer patients.”

Jo Grey, CEO and Chair of Trustee Board, AMEND

If you would like free copies for your patients, please email books@btf-thyroid.org with details.

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REFERENCES

Clinicians rely on the latest research evidence to support their treatment decisions and ensure patients receive the best evidence-based care. Research is a fundamental part of the NHS, and all organisations involved in delivering care are obliged, through the NHS constitution, to facilitate research within their organisations.

The National Institute for Health Research (NIHR), through its Clinical Research Network (CRN), provides some of the resources and infrastructure to enable this to happen. Read on to understand how the CRN works and how to access support for your research study. You will also learn about new initiatives that the NIHR CRN is undertaking in partnership with the Society for Endocrinology, to develop and promote research in endocrinology, metabolic disease and obesity.

WHAT SUPPORT DOES THE CRN OFFER RESEARCHERS?
The CRN’s Study Support Service helps to plan, set up and deliver research in the NHS. In the early stages, the Service might advise researchers about study feasibility and attribution of research costs, or help identify appropriate research sites. Once a study is funded and assessed as eligible for CRN support, local CRN teams may work closely with study teams in a number of ways, to ensure that recruitment targets are met within the planned time frame. Examples include provision of CRN-employed research nurses/health professionals to aid recruitment of subjects, as well as proactive performance-monitoring activities such as troubleshooting of barriers to recruitment, and sharing of good practice. For more information see www.nihr.ac.uk/funding-and-support/study-support-service.

‘Many endocrine conditions are under-represented in UK clinical research. The CRN is working together with the Society for Endocrinology’s own Endocrine Networks to encourage researchers to collaborate.’

WHAT TYPES OF STUDIES ARE SUPPORTED?
To be eligible for support, the research must contribute to generalisable new knowledge which is of clear value to the NHS and take into account the NHS’s needs and realities. In practice, this means that there must be clearly defined research questions which will be tested with rigorous methodology. Audits, biobanks and local service evaluations and needs assessments would generally be excluded.

If the research is not sponsored by industry, the funding of the study must have been awarded in open competition across England and have been subject to high quality peer review. In the case of investigator-initiated, commercially funded studies (i.e. funded but not sponsored by industry), the funder is required to confirm that the funding opportunity was open to all qualified researchers in England, even if there was no formal structured competition leading to its award, and the sponsor is required to confirm that appropriate peer review has taken place.

Studies sponsored by industry will not be subject to the open competition and peer review requirements, but will be reviewed for feasibility prior to receiving CRN support, although it is expected that the support costs for commercial research will be fully recovered from industry. Note that all research studies must be in receipt of funding to meet all research costs before they can be considered for CRN support.

CURRENT PORTFOLIO
The CRN’s portfolio of ‘Metabolic & Endocrine’ studies usually includes about 80 open studies at any one time. In 2016–2017, over 4,400 patients were recruited into clinical research studies in the portfolio.

Approximately one-third of the portfolio is made up of studies on rare inherited metabolic disorders, such as glycogen storage diseases and alkaptonuria. These are generally run by specialist centres with an interest in these disorders. Between one-quarter and one-third are on obesity. The remainder are studies into what would be considered general and specialist endocrinology, such as thyroid disease, Cushing’s syndrome and polycystic-ovary syndrome. About a quarter of all studies are commercially funded.

EXPANDING UK ENDOCRINE AND METABOLIC RESEARCH
Compared with some other specialities (such as cancer, cardiovascular disease and diabetes), endocrine research makes up a smaller portfolio, with many studies in rare diseases. (These are defined by the Medical Research Council (MRC) as conditions that affect fewer than 5 in 10,000 people.)

It therefore makes sense for studies to be collaborative and involve as many sites as practical to achieve the study aims. Some examples of highly successful observational studies in endocrinology that have involved many sites include the adult growth hormone database, the inherited disorders of sexual development study (I-DSD), and the genetics of endocrine tumours (the AIP study).

Improvement in the proportion of ‘Metabolic & Endocrine’ studies from recruitment to time and target (RTT).

Improvement in the proportion of ‘Metabolic & Endocrine’ studies from recruitment to time and target (RTT).
GENERAL NEWS

Despite these successes, and an increase in the proportion of studies recruiting to time and target (see Figure), it is recognised that many endocrine conditions are under-represented in UK clinical research. Consequently, the CRN is working together with the Society for Endocrinology’s own Endocrine Networks to encourage researchers to collaborate in writing applications for clinical research studies for NIHR and other major funders.

There will be an opportunity for the Endocrine Networks to meet during the forthcoming Society for Endocrinology BES conference in Harrogate in November. I encourage all clinicians who are interested in being involved in research (there is no requirement to be currently research-active) to come along and help generate and discuss ideas for new research projects in your own area of interest (see Table and advert below).

A networking event with key industry partners is also anticipated. We hope this could encourage new interactions between researchers and industry, so that pharmaceutical and device companies can consider opportunities to work with UK-based endocrinologists. It will also provide an opportunity for researchers to discuss their own ideas and the needs of their patients with industry partners.

JOHN P H WILDING
National Specialty Lead for Metabolic and Endocrine Disorders
NIHR Clinical Research Network

If you would like to get involved or if you have any ideas for new research studies that would benefit from this collaborative initiative, please contact crnmetabolicendocrine@nihr.ac.uk.

Areas of interest of the Society’s Endocrine Networks.

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<thead>
<tr>
<th>Network</th>
<th>Co-ordinators</th>
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<tr>
<td>Adrenal &amp; Cardiovascular</td>
<td>Jeremy Tomlinson (Oxford) &amp; Eleanor Davies (Glasgow)</td>
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<tr>
<td>Bone &amp; Calcium</td>
<td>Duncan Bassett (London) &amp; Colin Farquharson (Edinburgh)</td>
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<tr>
<td>Endocrine Neoplasia Syndromes</td>
<td>Raj Thakker (Oxford) &amp; Paul Newey (Dundee)</td>
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<tr>
<td>Metabolic &amp; Obesity</td>
<td>Barbara McGowan (London) &amp; Kevin Murphy (London)</td>
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<td>Neuroendocrinology</td>
<td>Waljit Dhillo (London), Marta Korbonits (London) &amp; Giles Yeo (Cambridge)</td>
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<td>Reproductive Endocrinology &amp; Biology</td>
<td>Stephen Franks (London) &amp; Andrew Childs (London)</td>
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<tr>
<td>Thyroid</td>
<td>Petros Perros (Newcastle upon Tyne) &amp; Carla Moran (Cambridge)</td>
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Endocrine Networks present: 
RESEARCH INCUBATOR MEETINGS

Do you have an innovative research idea? Do you need access to resources, databases or collaborators to attract funding and get your research under way?

Then apply for a slot in the Research Incubator meetings at this year’s SfE BES conference.

7-8 November 2017

WWW.ENDOCRINOLOGY.ORG/EVENTS/SFEBES2017
STEPHEN LINDSAY JEFFCOATE

Stephen Jeffcoate was the eldest of four sons born to a Liverpool gynaecologist, TNA (later Professor Sir Norman) Jeffcoate, and his Manx wife, Josephine. He went to school in Liverpool and later obtained first class honours in medicine at the University of Cambridge. He completed his medical studies at St Thomas’ Hospital in London, but chose to focus his career on clinical biochemistry. His dominant interests lay in the standardisation of hormone measurement and in making the results of reliable assays widely available for clinical practice.

He first developed quality assessment schemes for luteinising hormone (LH) and follicle-stimulating hormone (FSH) while working at St Thomas’ Hospital. But, when he was appointed Head of Biochemical Endocrinology at the Chelsea Hospital for Women in 1975, he was invited by the World Health Organization (WHO)’s Human Reproduction Programme to help standardise measurement of reproductive hormones on an international basis. This required the development and production of materials and methodologies for the measurement of LH, FSH, prolactin, oestradiol, progesterone, testosterone and cortisol, as well as their distribution to some 150 laboratories worldwide, and associated training and external quality assessment (EQA) schemes. The assay systems he developed were used by WHO for almost 25 years and made a major contribution to research in human and animal reproduction. His department at Chelsea was designated as the WHO Collaborating Centre for Research in Human Reproduction.

Together with Keith Ferguson, Steve also ran UK EQA Schemes for LH, FSH and prolactin. They developed the kits for these hormones, and supplied the majority of UK laboratories during the 1980s.

Steve enjoyed teaching and was a stimulating lecturer and mentor. He organised many training courses internationally, and frequently acted as a consultant to the WHO and the International Atomic Energy Agency (IAEA), serving regularly on expert committees. He was author and co-author of several specialist books, including The Endocrine Hypothalamus (1978) and Efficiency and Effectiveness in the Endocrine Laboratory (1981; later translated into Spanish, Mandarin, Thai and Russian), as well as almost 200 scientific papers.

In 1986, he was appointed Head of the Endocrinology Division of the National Institute of Biological Standards and Control (NIBSC) in Hertfordshire, but opted to take early retirement in 1993. He then served as a consultant to several major pharmaceutical companies and, through Clinical Pathology Accreditation, continued to be involved in the development of laboratory and EQA Scheme standards.

Steve’s horizons had, however, never been restricted to his professional training. He had many interests in literature and the arts, and had always read voraciously (and at extraordinary speed). Following retirement from NIBSC, and under the guidance of his third wife, Gail, he developed interests in ecology and wildlife, particularly in butterflies. He was Chair of the National Council of the charity Butterfly Conservation from 1999 to 2003. Under his leadership the charity moved to Dorset, increased its focus on conservation and enlarged its specialist and administrative staff, enabling it to expand to the 30,000-strong membership it has today. He was among the co-authors of the much-cited Millennium Atlas of Butterflies in Britain and Ireland (2001) and he himself became an authority on the ecology of the rare, and declining, wood white butterfly (Leptidea sinapis).

However, Steve also had a parallel interest, in the life of an earlier medical polymath, Sir Frederick Treves – the London surgeon now best known for delaying the 1902 coronation of Edward VII by operating on him for ‘perityphlitis’ (appendix abscess), and for his care of Joseph Merrick, the ‘Elephant Man’. Treves, too, had retired early from his medical career before going on to write a series of books on literature and on travel. Steve retraced several of Treves’ journeys, including those in France, Switzerland and Italy. He also followed the steps of Treves across South Africa, where he had served as a military surgeon in the two Boer Wars. One of Steve’s last publications in a medical journal appeared in The Lancet in 2000 with a characteristic play on words in its title ‘The retrieval of Ladysmith’. Sadly, the intended biography of Treves was never completed.

He took up long distance walking in his sixties. Travelling alone along the GR5 walking route in France from Nice to Lake Geneva, and also on the GR10 along the length of the Pyrenees from the Atlantic to the Mediterranean, he raised more than £10,000 for Butterfly Conservation. He later completed (on his third attempt) the tough GR20 in Corsica.

‘The assay systems he developed were used by WHO for almost 25 years and made a major contribution to research in human and animal reproduction.’

Steve had never lost his affection for his mother’s homeland, the Isle of Man, and spent increasing time there in the last 15 years of his life. He joined the wildlife community and was chair of the Manx Wildlife Trust from 2010 until 2013.

His recent years were clouded by repeated admissions to hospital, but he had rallied and was regaining much of his strength and independence, together with his characteristic good nature and sensitivity, when he suddenly developed an unrelated illness and died unexpectedly within 24 hours in March this year, aged 77. Steve is survived by his third wife, Gail, two of his brothers, three children from his earlier marriage to Jen, and six grandchildren.

SAULAT SUFI & WILLIAM JEFFCOATE
Here is the latest highlight from our journal Cover Art Competition, showcasing the best images in endocrinology.

**COVER IMAGE FROM ENDOCRINE-RELATED CANCER**

**JULY 2017**

The image depicts expression of the purinergic ligand-gated P2X7R ion channel in cultured adamantinomatous CP tumour (aCP) cells. Immunofluorescence shows positive staining for P2X7R (red) along with DAPI (blue) in tumour cells. From Nie et al. 2017 Endocrine Related Cancer 24 287–296. Credit: J Nie, G-I Huang, S-Z Deng, Y Bao, Y-W Liu, Z-P Feng, C-H Wang, M Chen, S-T Qi & J Pan (Southern Medical University, Guangzhou, China).
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