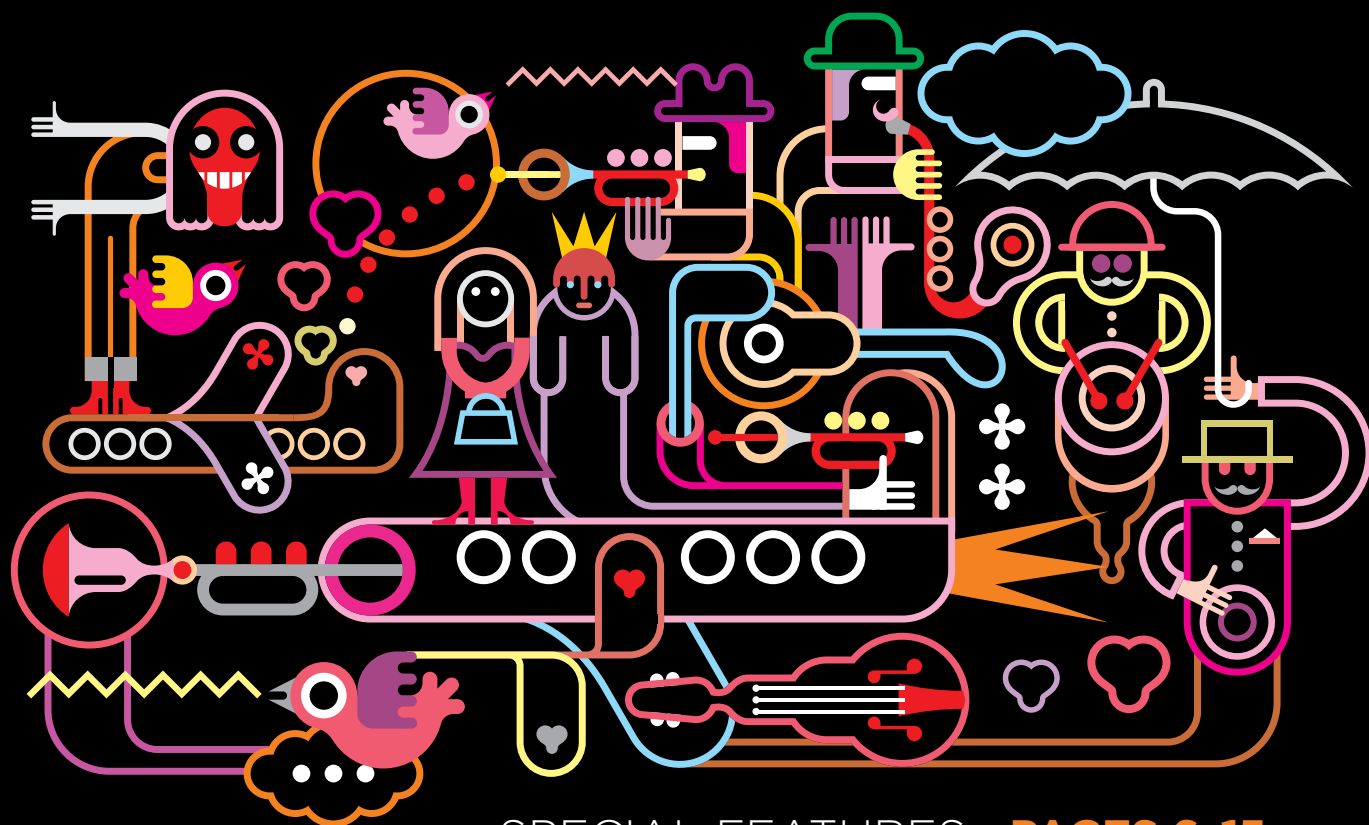


THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

ENDOCRINOLOGY ACROSS THE LIFESPAN



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A WORD FROM THE EDITOR...



So as the days get longer and our vitamin D levels start to replenish, we provide you with your essential summer 2015 holiday endocrine reading. The general election seems like a distant memory, Arsenal have hopefully just won the FA Cup, and we look towards Andy Murray having a good run at Wimbledon (he's back on form now he's tied the knot with Kim). The theme of this edition is 'Cradle to Grave' and it reminds us how endocrinology spans the whole cycle of life.

Yet again, we have managed to secure the highest calibre of authors covering a plethora of topics including fetal programming, the control of puberty, the genetics of pituitary development, short stature, the effect of the ageing population on our NHS and the science behind the elixir of youth. Steve Shalet is the subject of this edition's interview, which is fitting as much of his work has been on the importance of following the progress of children into adulthood and beyond.

We have an energetic new team of writers who have lots of good ideas. I'm particularly grateful to John Ratcliffe for his 'Letter to the Editor' which gives his perspective on the importance of laboratory and clinical collaboration for endocrine advancement – please keep this sort of thing coming. I continue to believe that we are lucky to be involved in a specialty that is both interesting and fun, and hope that this magazine brings us all together in some small way.

Happy reading and even happier holidays!

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

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

Deadline for news items for the Autumn 2015 issue: **13 July 2015**.

Deadline for news items for the Winter 2015 issue: **21 September 2015**.

Front cover image ©SHUTTERSTOCK



JOIN OUR TEAM: NEW ASSOCIATE EDITOR NEEDED

Could you be *The Endocrinologist's* new Associate Editor? We're looking for a clinician to join the Editorial Board as Associate Editor, starting in January 2016. You should have a passion for communicating endocrinology to your peers, with the drive to make sure that *The Endocrinologist* continues to develop as the premier magazine for endocrinologists.

The initial term of office is 2 years, with an expectation that the post holder will progress to the position of Editor of the magazine for a further 2 years subsequently. You will be expected to attend two meetings per year, with additional work conducted via email.

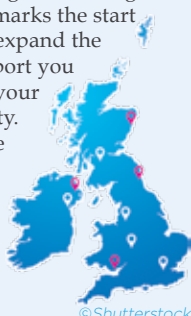
You can find more information and application forms at www.endocrinology.org/endocrinologist. The application deadline is 30 June 2015. Please send any informal enquiries to jennie.evans@endocrinology.org.

NEW MAP OF UK ENDOCRINOLOGY

The Society's new interactive 'UK Map of Endocrinology' is set to provide vital information about the location of current endocrine research. It will also include links to relevant individuals – identifying those that lead the current Society Endocrine Networks.

You will benefit from this new service whether you are a student looking for a PhD or a principal investigator looking for future collaborations. It marks the start of an ongoing project to expand the career development support you already receive through your membership of the Society. It will also strengthen the vital UK Endocrine Networks.

Further details about this project will follow shortly.



TOP AWARD FOR Sfe BES 2014!

The Society for Endocrinology BES conference 2014 recently won top honours at the national Association Excellence Awards 2015. The Sfe BES conference is the Society's annual flagship event, and was voted best association conference outside London. The award recognises excellence in the work of professional associations and how they serve their members.

The judges commented, 'This was a very good entry with some highly innovative measures introduced this year which certainly helped to drive up attendance. Good use of social media and emerging technologies to engage with the audience. A thoroughly well researched and well organised event.'

We are sure you will join us in extending congratulations to the Programme Committee and the office team who worked so hard to make this event a great success.

HELP US IMPROVE!



Are you involved in Society activities?

How informed do you feel?

Do you have other professional needs that we could help meet?

A few minutes of your time will help us greatly. Please visit the member area of our website to complete the online survey.

THREE CHEERS FOR JULIE!

The Society extends its warmest congratulations to Julie Cragg, our Society Services Manager, who recently celebrated her 20th anniversary of working at the Society. Many of you will know how integral Julie has been to the Society's success and how she has worked tirelessly to support members, run committees and manage grants. Here's to the next 20 years, Julie...



Julie Cragg



SOCIETY CALENDAR

2-4 November 2015
**SOCIETY FOR
ENDOCRINOLOGY
BES CONFERENCE
2015**
Edinburgh

see
[www.endocrinology.org/
meetings](http://www.endocrinology.org/meetings) for full details



GRANT AND PRIZE DEADLINES

4 MAY-6 JULY 2015
**Sfe BES REGISTRATION
GRANTS**

15 JUNE-13 JULY 2015
**UNDERGRADUATE
ACHIEVEMENT AWARDS**

15 JULY 2015
TRAVEL GRANTS

27 NOVEMBER 2015
EARLY CAREER GRANTS

27 NOVEMBER 2015
EQUIPMENT GRANTS

see
[www.endocrinology.org/
grants](http://www.endocrinology.org/grants) for full details of
all Society grants

WITH REGRET

We were saddened to hear news of the death of Barry Furr. Barry played an important role in the Society and was Chairman from 1993 to 1996. The Society extends its condolences to Barry's family and friends. A full obituary will appear in the next issue.

We are also sorry to announce the deaths of Society members Mohammad Ghatel from Imperial College London and Wolfgang Jochle from New Jersey, USA.

CONGRATULATIONS

Derek Renshaw, a member of the Society's Science Committee, has taken up the post of Professor of Applied Biological Sciences at Coventry University.

Stephanie Baldeweg, a member of the Society's Public Engagement Committee, was recently awarded the Chairman's Medal for Excellence in Education and Training by University College Hospitals London.

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

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



JOURNAL OF ENDOCRINOLOGY

Glucocorticoids and brown fat: good and bad news?

Recently, data indicating that thermogenic brown adipose tissue (BAT) has a relevant metabolic role in human health have grown dramatically. Although the effects of excessive glucocorticoids (GC) upon white adipose tissue (WAT) and body weight are well recognised, much less is known about the effects of GC on human BAT.

Barclay *et al.* used cells cultured from supraclavicular BAT of patients undergoing neck surgery to study GC effects on growth, development and function of brown adipocytes. Dexamethasone significantly increased brown adipocyte proliferation, expression of uncoupling protein 1 (UCP1)

and oxygen consumption rate (OCR), but significantly inhibited the ability of isoprenaline to increase UCP1 expression and OCR.

Although these small *ex vivo* studies cannot truly mimic the net effect of GC on BAT activity *in vivo*, there appears to be a complex effect whereby GC may increase BAT mass and metabolic activity, but also downregulate the oxidative response of brown adipocytes to adrenergic stimulation. Metabolic imaging of brown adipocyte depots in the neck fat of patients with GC excess may be highly informative.

Read the full article in *Journal of Endocrinology* **224** 139–147

JOURNAL OF MOLECULAR ENDOCRINOLOGY

MCT8 function is modulated by dimer formation

The monocarboxylate transporter 8 (MCT8) is a member of the major facilitator superfamily (MFS). MCT8 is a membrane-spanning protein facilitating translocation of iodothyronines. Several pathogenic mutations have been identified in MCT8, with affected patients suffering primarily from mental retardation and severe muscle hypotonia.

It is thought that MCT8 forms a dimer, and so one property potentially modulated by a mutation may be oligomeric organisation. Fischer *et al.* investigated the relationship between 14 naturally occurring mutations of MCT8 that have been identified in affected patients. Four mutations close

to the translocation channel inhibited dimerisation, three mutations in the transmembrane domain helix 2 led to increased dimerisation and the remaining seven demonstrated similar dimerisation ability to wild type.

This study indicates a link between the functions (substrate transport) and protein organisation (dimerisation) of MCT8. Understanding the regulation of the membrane transport of steroid hormones is an important aspect of their action and this study may be relevant to other members of the MFS.

Read the full article in *Journal of Molecular Endocrinology* **54** 39–50

ENDOCRINE-RELATED CANCER

Early marker for prostate cancer initiation

Although powerful evidence exists for the late-stage genomic changes that occur in prostate cancer, little is understood about the early initiation events that turn benign prostate cancerous.

Massie and colleagues have identified that promoter hypermethylation of the transcription factor *HES5* is an early event in prostate tumourigenesis. This epigenetic alteration occurred in 86–97% of prostate cancer cases, and treatment with a demethylating agent increased *HES5* expression and downregulated its transcriptional target *HES6*. These results are consistent with the functional silencing of the *HES5* gene in prostate cancer.

Furthermore, this work identifies and tests a transcriptional model involving the androgen receptor, the oncogene *ERG*, *HES1* and *HES6*, which suggests an impact of *HES5* silencing on tumourigenesis as a starting point for future functional studies.

This research highlights the importance of *HES5* silencing as an early and frequent event in the evolution of prostate cancer. This may act as a biomarker or a starting point for targeted intervention strategies in prostate cancer patients.

Read the full article in *Endocrine-Related Cancer* **22** 131–144 (OA)

ENDOCRINE HIGHLIGHTS

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



Fast-moving feeding circuits

The hypothalamus is vital in controlling food intake and energy expenditure. Agouti-related protein (AgRP) and pro-opiomelanocortin (POMC) neurones are well-characterised hypothalamic populations with opposing roles in the control of feeding. Current thinking places circulating hormones and nutrients as the primary drivers controlling the activity of these cells.

Chen and colleagues have shown that this hypothalamic feeding circuit also receives 'real-time' information about food availability in a manner distinct from the circulating peripheral signals. They used an optical fibre to record total fluorescence of a population of neurones expressing a calcium reporter, allowing analysis of real-time activity of a molecularly defined population of hypothalamic neurones. Their data indicated that both AgRP and POMC neurones are strongly regulated by the sensory detection of food alone, via neural inputs which activate before any food is even consumed.

This mechanism may play a role in halting foraging behaviour once food has been located. Whether similar mechanisms exist in humans remains to be determined, but these data add another layer of complexity to a crucial feeding circuit and highlight a potential node whereby homeostatic and immediate real world information may converge.

Read the full article in *Cell* **160** 829–841

CLINICAL ENDOCRINOLOGY

Dexamethasone suppression test with desmopressin to diagnose recurrent Cushing's

UK readers will be familiar with the use of 24-h urinary free cortisol and overnight dexamethasone suppression tests, but perhaps less so with the desmopressin test.

The coupled dexamethasone-desmopressin test (CDDT) consists of 1mg dexamethasone given at midnight, then morning measurements of adrenocorticotrophin (ACTH) and cortisol before and after an intravenous injection of 10µg desmopressin. The test is positive when ACTH and cortisol both rise by more than 50%.

Le Marc'hadour *et al.* assessed which test is best for determining relapse of treated Cushing's disease. The CDDT had an impressive negative predictive value of 100% and the authors report that, in cases of relapse, it becomes positive significantly earlier than loss of circadian rhythm of cortisol secretion or failure of dexamethasone suppression.

They propose that it be performed annually in the first 3 years post-operatively, and the results used to determine the intensity of long term follow up.

Read the full article in *Clinical Endocrinology* at doi:10.1111/cen.12739

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Hypothyroidism and non-cardiogenic pulmonary oedema

Al-Sofiani *et al.* report the case of a 42-year-old woman who presented to the emergency department with shortness of breath for the preceding week. She had recently contracted an upper respiratory tract infection and had a history of asthma and hypothyroidism.

The patient was admitted as a case of cardiogenic pulmonary oedema secondary to possible viral myocarditis, based on clinical and radiological findings. However, this initial diagnosis was changed to non-cardiogenic pulmonary oedema following further tests that showed a normal brain

natriuretic peptide level, along with normal ejection fraction on the echocardiogram. Subsequent questioning of the patient revealed a pattern of symptoms suggestive of sleep apnoea syndrome.

The authors propose that sleep apnoea syndrome was a contributory link between the patient's hypothyroidism and non-cardiogenic pulmonary oedema.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* 2015 EDM150014 (OA)

ENDOCRINE CONNECTIONS

Water deprivation test performance in diagnosis of diabetes insipidus

The water deprivation test is the gold standard in differentiating between central or nephrogenic diabetes insipidus (DI) and primary polydipsia (PP) in patients with polyuria and polydipsia. However, few studies have examined the diagnostic performance of this test.

In this retrospective cohort study, de Fost *et al.* compared initial test results with final clinical diagnosis. They found the best parameter for diagnosis of PP was a urine osmolality >680mOsmol/kg after water deprivation

(sensitivity and specificity 100%). The original cut-off value of 800mOsmol/kg resulted in a lower accuracy. Arginine vasopressin (AVP) levels did not differ between patient groups and did not distinguish between central DI, nephrogenic DI or PP.

This suggests that differentiating between central and nephrogenic DI should be based on clinical judgement rather than AVP levels.

Read the full article in *Endocrine Connections* 4 86-91 (OA)

POMC and the marijuana munchies

Ingestion of marijuana causes an uncontrollable urge to eat, known as 'the munchies'. Koch and co-workers have shown that this drive is controlled by pro-opiomelanocortin (POMC)-producing neurones in the hypothalamus. All previous evidence has suggested their involvement in appetite suppression, but this study calls that function into question.

In the fed state, POMC neurones are activated to produce α -melanocyte-stimulating hormone (α MSH), which in turn promotes feelings of satiety. When POMC or α MSH synthesis or action is inhibited in mice, there is a significant increase in hyperphagia, or over-eating, and resultant morbid obesity. Koch and colleagues examined the effects of the cannabinoid mimic arachidonyl-2'-chloroethylamide (ACEA), which prompts over-eating, in mice. Animals given ACEA over-ate. This hyperphagia was associated with POMC neurone activation. When POMC neurone activity was experimentally inhibited, the animals no longer exhibited ACEA-induced overeating, which confirmed the cells were essential for the behaviour.



The key finding came when POMC neurones were treated with ACEA in culture. Instead of producing and secreting α MSH, they secreted β -endorphin - a hormone which increases appetite. Whether this mechanism is also key to getting 'high' on cannabis remains to be determined.

Read the full article in *Nature* 519 45-50

Thyroid eye disease and antiretroviral HIV therapy

Thyroid eye disease (TED) secondary to Graves' is a well recognised autoimmune inflammatory condition. For those individuals with co-existent HIV infection, the introduction of highly active antiretroviral therapy (HAART) can potentially precipitate a significant immune reconstitution syndrome, posing its own unique challenges in practice.

Edmunds and colleagues have undertaken a cross-sectional study of all patients with both Graves' and HIV to determine the frequency, the presentation of TED and the course of disease, in order to identify management issues and solutions. Overall, they found that TED was uncommon, but the patients with TED and HIV often faced drug interactions with anti-thyroid and immunosuppressant treatments versus HAART. Future studies undertaking multi-centre surveillance are called for.

Read the full article in *Journal of Clinical Endocrinology & Metabolism* 100 779-787

Oxytocin in gaze-mediated canine-human bonding

The mutual bond between humans and dogs has been known for thousands of years, but we are only just beginning to understand the underlying biology. Gaze-mediated bonding is mediated by oxytocin in humans. Nagasawa *et al.* examined whether a similar mechanism occurs when a dog stares into its owner's eyes.

Levels of oxytocin increased in owners when gazing into their dogs' eyes, a response that was mirrored in the dogs themselves. Notably, this response is not found in wolves, who generally avoid eye contact with humans. In a second experiment, female dogs were found to stare at their owners for longer after receiving an oxytocin nasal spray (an effect not seen in males).

The release of oxytocin by dogs and their owners in response to mutual gaze may contribute to the social bond formed between them, a mechanism which could have evolved during the domestication process.

Read the full article in *Science* 348 333-336

DEVELOPMENTAL PROGRAMMING: WHAT DOES THE FUTURE HOLD?

WRITTEN BY JONATHAN SECKL



Endocrinologists will be aware of the emerging science of developmental programming. Contemporary interest was sparked in the 1980s, when the late David Barker observed that lower birth weight (assiduously recorded and retained in a handful of NHS hospitals in England) correlated with a higher subsequent incidence of hypertension, diabetes, cardiovascular deaths and neuropsychiatric disorders in adult offspring.

These observations, repeated across the globe, have survived the rigours of systematic review and meta-analysis. The effects reflect continuous relationships through the normal range of birth parameters, and seem especially marked in infants who show postnatal catch-up growth. This suggests that factors in the environment restraining the fetus's intrinsic growth potential, or a mismatch between intrauterine and postnatal growth, are particularly adverse.

CAUSES

How might the link between fetal growth and later disease be explained? Genetics is an obvious candidate. Genes encode the major fetal growth factors. The same genes might, through pleiotropic actions, also underpin later pathogenesis. Obvious candidates include insulin-like growth factors and their signalling pathways. However, studies of identical twins, that suggest the smaller at birth has a greater incidence of adult disease, and recapitulation of programmed phenotypes by environmental challenges during development in genetically identical animals, demonstrate that genetics is unlikely to be the whole explanation. Nonetheless, the preservation of the programming phenomenon through much of the animal kingdom, and thus hundreds of millions of years of evolution, implies genetic maintenance of the underlying biology through the eons.

Alternative proximate explanations invoke the environment and its interaction with the genome during critical sensitive stages of development. In mammals, this is the intrauterine and postnatal environment, in birds and lower vertebrates it is the egg's environment. What factors might be at play?

Many groups have examined nutrition. Maternal under-nutrition or over-nutrition in mammalian gestation affects fetal growth and exerts persisting effects on the offspring in a variety of models and human observational studies. Other explanations pertinent to mammals include fetoplacental hypoxia and/or under-vascularisation, environmental toxin exposure, immunological and inflammatory challenges and stress/glucocorticoid over-exposure.

The last has been particularly useful, since the mechanisms of glucocorticoid action through transcription factor receptors offer mechanistic pathways for dissection. Moreover, glucocorticoids are a terminal differentiation signal for many fetal tissues, instructing developing cells to stop dividing and differentiate into mature tissues ready for independent existence. This is the rationale for clinical administration of glucocorticoids in threatened pre-term labour, efficaciously accelerating fetal lung maturation.

‘Increasing data have suggested that programmed effects may not just persist through the lifespan but can be “inherited” by the next generation’

These hypotheses are not mutually exclusive. Glucocorticoids/stress reduce maternal food intake, maternal under-nutrition or cytokines attenuate placental 11 β -hydroxysteroid dehydrogenase type 2, which forms a ‘fetal barrier’ to maternal glucocorticoids, malnutrition activates the fetal hypothalamic-pituitary-adrenal axis, maternal challenges alter fetoplacental vascularisation, etc., in a range of models, all of which show rather similar programmed phenotypes in adult offspring.

MECHANISMS

However this begs the question of how a transient signal during early development can have persisting impacts throughout the lifespan. There are two broad categories of mechanism by which early life events can have a permanent impact on the tissue structure and function of the offspring.

The first is differences in cell number in an organ. This occurs in a variety of programming models, for instance determining pancreatic islet beta cell mass and hence glucose-insulin homeostasis, nephron number and hence renal function/blood pressure homeostasis, and sexually dimorphic structures in the brain underlying reproductive strategies.

A second fundamental mechanism involves alteration of the set-point of gene expression within individual cells. Again, much evidence supports developmental programming of persisting changes in gene expression in a tissue-specific pattern. So how can gene expression changes be maintained for the lifespan, particularly in long-lived species including our own?

EPIGENETICS

The current popular explanation is epigenetics. Epigenetics, a term coined in the mid 20th century by Conrad Waddington in Edinburgh, refers to chemical modifications to chromatin which may alter



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transcription without changing the underlying DNA sequence. Some include the effects of non-coding RNAs within this term.

Two epigenetic processes in particular have been investigated in programming. Histones comprise a set of proteins around which DNA can be tightly wound, usually blocking transcription. They are subject to a series of chemical modifications, notably acetylation and methylation of specific lysine residues. Whilst these changes are often short-lived and mark inactive or active DNA transcription, some are persistent. Recent data in eukaryotic fission yeast suggests that histone3-lysine9 methylation persists through mitosis, and even meiosis, if a key modifying enzyme is deleted. Whether or not this occurs in vertebrates and can be modulated by early events is unexplored.

A second process involves covalent changes to DNA itself. Methylation of cytosine residues generally makes these unavailable for binding by transcription factors, attenuating transcription, though some DNA-binding proteins seek methylcytosine. More recently, hydroxymethylation of cytosine has been discovered and has been associated with greater transcriptional activity, notably during development. A growing number of studies show that changes in methylation in promoter regions of genes during development may persist through mitosis and for much of the lifespan. These effects are often tissue-specific and sometimes, but not invariably, have been correlated with changes in cognate gene expression. Thus, an environmental challenge early in development may alter the likelihood of transcription of a particular promoter, affecting the progeny of that cell. How a tissue becomes sensitive or resistant to such challenges may reflect what is developing at the time and/or the simultaneous presence of specific DNA-binding proteins.

Increasing data have suggested that programmed effects may not just persist through the lifespan of the animal but can be 'inherited' by the next generation. Whilst a female offspring of an exposed pregnancy with the programmed phenotype may herself present an abnormal uterine environment leading to re-exposure of her offspring, paternal inheritance implies a genetic or epigenetic process. Major challenges, such as toxin exposure, can lead to persisting effects passing through the male line into multiple generations, but these might be classical genotoxicity. More commonly, maternal nutritional or stressful challenges can be passed down the paternal line but persist only for a couple of generations (exposure in late gestation impacts directly upon the developing fetus, and also directly upon its developing germ cells and thus the second generation, without true intergenerational inheritance).

Moreover, whilst the phenotype in the first and second generations appears similar, recent data show that the cellular mechanisms and associated epigenetic marks are distinct, at least in some models, implying strong selection for recapitulating the programmed phenotype into a second generation. This is perhaps unsurprising in short-lived species where a challenging environment is likely to affect several generations, but its rationale is not quite so obvious in long-lived humans. Perhaps the genetic underpinnings are too vital to be expunged lightly.

The mechanistic differences between generations suggests that any enthusiasm for neo-Lamarckism (named after the 19th century biologist who proposed that evolution progressed by inheritance of characteristics acquired during the lifespan, superseded by Darwin's theory of evolution through natural selection) may be premature.

'Working out this interaction between the genome and the environment is crucial in our attempts to use this knowledge for health benefits'

Thus epigenetics reflects an interface between the developmental environment and the genome. Is that all we need to know? Well perhaps not. Crucial mechanistic studies of whether DNA and histone changes are sufficient for the whole programmed phenotype are far from complete. Also, recent data suggest that the sensitivity to epigenetic changes is substantially determined by the host genotype, suggesting epigenetics only has an impact in a gene-determined manner. Working out the details of this interaction between the genome and the environment is crucial in our attempts to understand programming and to use this knowledge for health benefits.

CLINICAL IMPLICATIONS

The possibility of determining the contributions of genetics, developmental epigenetics and adult environmental factors in a patient with, say, type 2 diabetes or depression, may facilitate targeted therapy. Fetal programming of elevated liver glucocorticoid receptor levels may underpin increased hepatic gluconeogenesis and hyperglycaemia. In adults, metformin, but not thiazolidinedione, corrects over-expression of hepatic glucocorticoid receptor. Since some epigenetic marks appear stable, newborn blood may afford a register of epigenetic risk, at least for leukocytes.

This affords a vision where genetic, epigenetic and environmental components of an individual's disease can be identified and treatment targeted to the causal factors. Epigenetic modifying drugs are under development and some, such as sodium valproate, are already in clinical use, albeit largely for other actions. A brave new world of discovery can be imagined for the basic endocrinologist, but there is an awful lot to understand before this exciting science may influence clinical practice.

JONATHAN SECKL

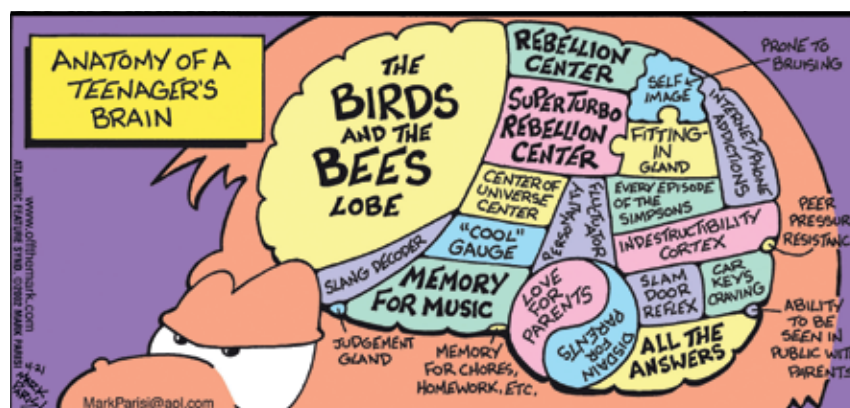
Vice Principal and Moncrieff-Arnott Chair of Molecular Medicine,
University of Edinburgh

PUBERTY: THE GATEWAY TO ADULthood

WRITTEN BY PETER CLAYTON



Puberty encompasses that period in a child's life when a surge in both sex and growth hormones results in the physical manifestations of pubertal development alongside the acceleration of statural growth. It occurs over the years when young people can be faced with a series of challenges: endless public examinations, establishing their own identity, perhaps leaving home, starting a job, and other key life events.



©Mark Parisi

It is therefore no wonder that mood swings and erratic and risk-taking behaviours are frequent during this phase of considerable hormonal and social change; in fact puberty has been referred to as a state of temporary madness, a description that will resonate with many parents.

So what controls this powerful process? We know much about the hypothalamic-pituitary-gonadal changes that occur as puberty starts, but what actually triggers puberty in the first place?

QUESTION #72: WHAT TRIGGERS PUBERTY?

In 2005, *Science* published a special edition entitled '125 questions: what don't we know?' The top question was 'What is the universe made of?' but, alongside that imponderable, at number 72, was 'What triggers puberty? Nutrition – including that received *in utero* – seems to help set this mysterious biological clock, but no one knows exactly what forces childhood to end.'

The last 10 years have seen much progress in understanding how genes, their protein products and the pathways they control might lead to pubertal activation, but the fundamental trigger remains elusive. Work in murine and primate models, and in humans, has used genome association studies to relate genes to key events in puberty, such as menarche, and disease models such as hypogonadotropic hypogonadism and precocious puberty. One new discovery is the kisspeptin pathway, which has been intimately related to the onset and development of puberty.

It is likely these significant advances will lead to new therapies to manipulate the pubertal process at a more physiological level than the relatively crude treatments we currently use: blocking gonadotrophin release when puberty is too early and replacing sex steroids when they are lacking, irrespective of the cause.

THE MEANING OF PUBERTY

Putting genes and trigger mechanisms to one side, what does puberty mean for an individual and how does it impact on clinical endocrinologists (both paediatric and adult)? Thinking in the context of 'cradle to grave', the successful journey through puberty is a young person's ticket to adulthood and the inevitable hormonal decline thereafter. For instance, there is no time in life when levels of growth hormone and insulin-like growth factor-1 are higher.

Puberty is considered to end at the achievement of full adult breast/genital/pubertal/axillary hair development, which occurs from the mid- to later teens. However, somatic development continues for longer, with peak lean and bone mass not fully accrued until the mid-20s, processes that depend on these high levels of sex and growth hormones. If puberty occurs too early, too late or not at all, there are major consequences for body and mind, which need to be 'fixed' with medical therapies.

CLINICAL CONUNDRUMS

Precocious puberty (that is, signs of puberty before 8 years of age in a girl or before 9 in a boy) is an emergency for the paediatric

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endocrinologist. A diagnosis must be made – is there an underlying pathology or is this idiopathic? And the process needs to be halted by therapy with a gonadotrophin-releasing hormone analogue until an acceptable age to resume pubertal development is achieved.

Concerns about delayed puberty are a very common reason for referral to paediatric endocrinology, and the most likely diagnosis is constitutional delay in puberty, which is usually associated with a delay in growth. Patience and/or a short course of sex steroids are all that is needed. However if gonadotrophins are absent or the gonads damaged, induction and maintenance of puberty with sex steroids will be required.

For a clinical scenario that is so common for endocrinologists, it is surprising that there is no consensus on the best approach and which sex steroid preparations to use, both for achieving full sexual development and optimising the chances of fertility and/or carrying a baby to term. For boys, testosterone injections are the most commonly used preparations, but topical agents are a useful alternative. For girls,

there is a range of synthetic and natural oestrogens that can be used, but evidence is poor regarding which results in the best bone mass accrual versus uterine development.

MANAGING THE MYSTERY

The triggers may remain a mystery, but there is no doubt that the process of going through puberty is a fundamental 'rite of passage' for every child. For those who go into puberty too early, we in endocrinology need to know how to stop it, while for those who are unable to make it through puberty spontaneously, we need to know when and how to take that person through this key phase of their life. Crucially, that young person needs to understand the implications for their later reproductive life. It is therefore imperative that paediatric and adult endocrine services are adequately connected to make this happen.

PETER CLAYTON

Professor of Child Health and Paediatric Endocrinology at the University of Manchester and Central Manchester University Hospitals Foundation Trust



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CONGENITAL DISORDERS OF PITUITARY DEVELOPMENT: MOLECULAR GENETICS AND MANAGEMENT

WRITTEN BY MEHUL DATTANI



Congenital hypopituitarism (CH) is a rare disorder with a reported incidence ranging from 1 in 3,000 for isolated growth hormone (GH) deficiency to 1 in 10,000 for more complex disorders. It is associated with significant morbidity and, if undetected or inadequately treated, mortality.

Hypopituitarism is often associated with other congenital abnormalities such as eye and midline forebrain defects (septo-optic dysplasia, SOD), cervical vertebral abnormalities, cerebellar abnormalities and sensorineural hearing loss. Recent advances in our knowledge of the molecular mechanisms underlying these disorders have led to improved understanding of the conditions, and improved management at the bedside. Many of the genes identified in association with hypopituitarism encode transcription factors – these bind to DNA and either activate or repress transcription of downstream target genes.

THE MOLECULAR BASIS OF CH

Congenital hypopituitarism was believed to be a sporadic condition, the aetiology of which remained largely unknown. At one point, it was thought to be the result of birth trauma. In 1992, elucidation of the molecular basis underlying two dwarf mouse models, namely the Snell and Jackson dwarfs, led to the identification of the first gene associated with hypopituitarism in humans, *PIT1* or, as it is now known, *POU1F1*.

POU1F1 AND *PROP1* MUTATIONS

This was the first example of a candidate gene approach in the elucidation of the molecular basis of CH. Both recessive and dominant mutations have been identified in this gene encoding a pituitary transcription factor and, indeed, the most frequent mutation identified is the heterozygous missense substitution p.R271W, which can be transmitted in a dominant manner from one generation to the next.

The phenotype consists of GH and prolactin deficiencies, with variable thyrotrophin (TSH) deficiency, in keeping with a role for *POU1F1* in the differentiation, proliferation and maintenance of somatotrophs, thyrotrophs and lactotrophs. Gonadotrophs and corticotrophs on the other hand are usually spared and so adrenocorticotrophin (ACTH) and gonadotrophin deficiencies are not associated with the phenotype.

A few years later, mutations in the pituitary-specific transcription factor *PROP1* (or prophet of *PIT1*) were described in a further cohort of hypopituitary patients, following the identification of the molecular basis of the Ames dwarf mouse, which is the result of a recessive missense mutation in *Prop1*. The phenotype of the affected patients was largely one of GH, TSH and prolactin deficiencies, but with the addition of gonadotrophin deficiency. Initially, it was thought that the corticotrophs were spared, but it is now clear that ACTH deficiency is very much a part of the phenotype. However, the phenotype can evolve and ACTH deficiency in particular could be a late event.

A further feature of the phenotype is the transient enlargement of the pituitary gland, when the possibility of a tumour may be raised. However, the size of the pituitary can wax and wane before its eventual involution. Generally, the phenotype of patients with *PROP1* mutations is that of GH, TSH, prolactin, ACTH and gonadotrophin deficiencies,

with a small anterior pituitary and a normally placed posterior pituitary. To date, *PROP1* deficiency seems to be the commonest genetic cause of hypopituitarism, accounting for 50–100% of familial cases, although only around 10% of sporadic cases are due to *PROP1* mutations.

HESX1 MUTATIONS

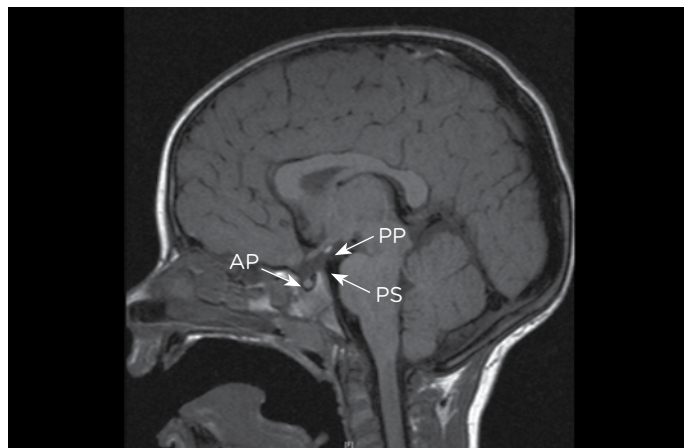
In 1998, the story became more complex with the identification of mutations in a transcriptional repressor gene called *HESX1*, initially in association with SOD, but later with GH deficiency and combined pituitary hormone deficiencies (CPHD) without midline or eye defects being added to the phenotypic spectrum.

SOD is a highly variable condition characterised by hypopituitarism, often including both anterior and posterior pituitary hormone deficiencies, in association with midline forebrain defects such as absence of the septum pellucidum and corpus callosum, and eye defects such as optic nerve hypoplasia and colobomas. Associated features include severe learning difficulties and autism. Only a small proportion (<1%) of SOD cases can be explained by *HESX1* mutations; the majority remain unexplained, implying the existence of mutations in other genes that are still to be identified and/or epigenetic/environmental factors. One curiosity that is not yet understood is the increased incidence of SOD in younger mothers.

HESX1 mutations may be dominant or recessive, and have also been associated with pituitary aplasia. Additionally, the mutations may be variably penetrant; i.e. the parent can carry the same heterozygous mutation yet may not manifest the phenotype. The posterior pituitary is often placed 'ectopically' in the tuber cinereum or along the pituitary stalk – this may reflect a maldevelopment.

LHX3 AND *LHX4* MUTATIONS

In 2000, recessive mutations in *LHX3* were described in patients with hypopituitarism and a short stiff neck with an abnormal cervical spine. Again, although it was initially thought that corticotrophs were spared, it is now clear that these patients will probably develop ACTH deficiency at some stage. Also, it has now been established that the majority of these patients exhibit a degree of sensorineural hearing impairment. The anterior pituitary may be small or occasionally



Ectopic posterior pituitary (PP) with anterior pituitary (AP) hypoplasia. Pituitary stalk (PS) is absent in this image. ©Mehul Dattani

enlarged, with the appearance of a microadenoma. The posterior pituitary is always eutopic, however.

This is in contrast to mutations in the related gene *LHX4*, which can be associated with highly variable phenotypes including CPHD (mainly GH deficiency) associated with anterior pituitary hypoplasia and an ectopic posterior pituitary and cerebellar abnormalities on magnetic resonance imaging. The mutations are heterozygous and variably penetrant, with parental carriers often showing no phenotype.

'We can only identify a genetic basis in around 15% of cases, suggesting that other genes remain to be identified'

OTHER MUTATIONS

More recently, duplications as well as loss of function mutations in the SRY-related gene *SOX3* have been associated with X-linked hypopituitarism, classically GH deficiency but also panhypopituitarism, as well as variable learning difficulties. We have recently described a persistent craniopharyngeal canal in association with a *SOX3* deletion.

Heterozygous mutations, usually *de novo*, in the related gene *SOX2* are associated with a complex phenotype consisting of learning difficulties, oesophageal atresia, severe eye abnormalities including anophthalmia, and hypogonadotrophic hypogonadism. *SOX2* has been shown to be implicated in the proliferation and maintenance of stem cells in the pituitary, and continues to be expressed in the postnatal and adult pituitary in a small population of progenitors, the role of which remains to be established.

Heterozygous mutations in *OTX2* are also associated with severe eye abnormalities in association with hypopituitarism, classically GH deficiency, whereas variably penetrant mutations in *GLI2* have been described in association with severe midline brain defects including holoprosencephaly in association with hypopituitarism and isolated CPHD without midline defects. The recent demonstration of a genetic overlap between hypopituitarism and Kallmann syndrome (*PROKR2*, *FGFR1*, *FGF8*, *CHD7*) has muddled the waters further.

Recent advances in genetic technology have led to the use of whole exome sequencing in the identification of novel candidate genes, and so this reflects a paradigm shift in approach. This approach has led to the identification of mutations in genes such as *IGSF1* associated with X-linked central hypothyroidism, and *ARNT2* associated with a severe recessive form of hypopituitarism, probably secondary to abnormal hypothalamic development, and vesico-ureteric reflux.

THE NEXT STEPS

Much has been achieved in terms of our understanding of hypothalamo-pituitary development and the aetiology of CH. On the other hand, we can only identify a genetic basis in around 15% of CH cases, suggesting that other genes remain to be identified. The use of whole exome and potentially whole genome sequencing may lead to an improved understanding of the condition.



In particular, it is likely that, as observed with Kallmann syndrome, mutations in more than one gene may lead to the variable penetrance, and hence phenotypic expressivity, of hypopituitarism and SOD. Many other questions will need a more basic approach, for example the aetiology of the pituitary masses associated with *PROT1* and *SOX2* mutations. Close collaboration between basic scientists and clinicians will be required to further the field.

'Understanding the molecular basis of congenital hypopituitarism can have an impact on its clinical management'

CLINICAL RELEVANCE OF MOLECULAR GENETICS IN CH MANAGEMENT

Understanding the molecular basis of CH can actually have an impact on its clinical management. For example, the identification of *POU1F1* mutations would rule out the possibility of ACTH and gonadotrophin deficiencies, whereas the presence of *PROT1* mutations might alert one to the probability of evolving ACTH deficiency, and encourage a more relaxed approach to the presence of a pituitary mass.

Although, at present, molecular analysis is offered in only a few centres on a research basis, it is likely that this addition to the diagnostic armamentarium for CH will be routine in the fullness of time.

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MANAGING IDIOPATHIC SHORT STATURE: TOWARDS A BALANCED VIEW

WRITTEN BY MARTIN SAVAGE



'Idiopathic short stature' (ISS) describes children who are short with no definable cause. ISS is not a specific diagnosis. In fact, the presence of an identifiable aetiology eliminates a child from this category.

In 2008, ISS was defined as short stature less than two standard deviations below the mean, normal growth hormone (GH) secretion and the absence of low birth weight, chromosomal abnormalities, syndromic features or chronic illness.¹ Management is problematic when the aetiology is unidentified.

A number of disorders, once labelled as ISS, have been redefined following molecular investigations. Examples are acid labile subunit (ALS) deficiency, and mild GH receptor and *SHOX* mutations. Borderline GH deficiency, GH neurosecretory dysfunction and short healthy parents are also potential causes. Hence, a range of sensitivities to growth-promoting therapies is seen in ISS children, as described in the 'continuum model' of GH-insulin-like growth factor-1 (IGF-1) axis defects.²

THE CASE FOR GROWTH-PROMOTING HORMONE THERAPY

In 1985, the emergence of Creutzfeldt-Jakob disease in children treated with human pituitary-derived GH led to the almost seamless introduction of recombinant human GH (rhGH). The availability of large quantities of rhGH, albeit at a high cost, was of certain benefit to GH-deficient children, but opened a Pandora's box of challenges in the child with non-GH-deficient short stature. ISS, of course, comes into this category. However, the hypothesis that pharmacological rhGH doses could safely induce clinical benefit in children with short stature due to a variety of causes was justifiably tested.

Well-designed studies, usually efficiently administered by rhGH-producing pharmaceutical companies collaborating with academic centres, were initiated in Turner syndrome and then ISS. Our knowledge of rhGH responses would be significantly smaller without collaboration with the pharmaceutical industry. The case for treating children with ISS was made on the basis that growth failure was comparable with that seen in GH deficiency and predictions of adult height showed a deficit which could induce physical and psychological disadvantages.

Studies of rhGH therapy in ISS were designed initially to demonstrate catch-up growth, rather than long term growth benefit. Predictably, children receiving pharmacological doses of 40–50 µg/kg per day grew faster than control subjects and had improved adult height predictions. Armed with efficacy and safety data, compared with results in untreated or placebo-treated controls, several pharmaceutical companies applied to the US Food and Drug Administration (FDA) for registration of ISS as a licensed rhGH indication. In 2003, approval was granted. Some ISS patients with low IGF-1 levels were included in the FDA approval of rhIGF-1 therapy for primary IGF-1 deficiency.²

REACTION TO ISS AS A LICENSED INDICATION FOR rhGH

When the FDA Advisory Committee voted in favour of licensing rhGH for ISS, there remained concern within the Committee that results

showing statistical differences between rhGH-treated and non-treated children might not be translated into real clinical benefit.³ Allegations of 'enhancement' rather than treatment were voiced, with pharmaceutical companies being accused of creating a diagnosis, i.e. ISS, to generate a new market for their products.⁴ In general, however, in the USA, the approval was welcomed and most paediatric endocrinologists initiated rhGH therapy in significant numbers of ISS patients.

Twelve years later, something of a trans-Atlantic cultural divide exists. Pharmaceutical company applications to the European Medicines Agency (EMA) for the same indication have been consistently rejected, with lack of quality of life data and the absence of a clear distinction between ISS and normality being the main reasons. European paediatricians are more conservative, and the long term adult height results have been correctly exposed as disappointing.⁵

SOCIAL PRESSURES OF SHORT STATURE

It would be easy to dismiss the psychological impact of short stature. Studies have failed to demonstrate a consistent psychological burden in healthy short children and there are no convincing data showing that rhGH therapy improves quality of life.

However there are tangible social pressures related to height in childhood. These have recently been described in South Korea, where children aspire to an adult height of 8–9 cm greater than the national average.⁶ Private clinics for stretching children thrive in South East Asia and thousands of healthy children in the Philippines take 'Cherifer', an algae-based chlorella growth factor, reputed to increase growth. The challenge of 'heightism', a perceived social disadvantage related to childhood and adult short stature, is here to stay. So how should endocrinologists respond?

BALANCED MANAGEMENT DECISIONS

In Europe, we can explain to families and patients that the 'benefits' of rhGH therapy in ISS have been carefully examined and have not been conclusively demonstrated. Reimbursement by national healthcare systems does not exist. However, we have all seen cases where there is auxological evidence of subnormal growth velocity and height below the parental target, who we believe would respond to rhGH therapy.

If therapy is available for such patients, there are a number of imperatives regarding their management.

First, the child's interest is paramount, which requires honesty from the clinician about

the uncertainty of the predicted growth response. A guarantee of clinical benefit may backfire if the response is disappointing, with the doctor being unwilling to admit an error of judgement and thus lose face. Secondly, a dose of rhGH sufficient to stimulate growth is indicated, i.e. ~50 µg/kg per day. There is no logic in using a replacement dose of ~25 µg/kg per day. Thirdly, a formal assessment of the child's response is essential at the end of year 1 of therapy. In all growth disorders, the response during year 1 correlates positively with the long term height gain.⁷ If a positive response is seen, i.e. an increase in height of more

'The challenge of "heightism", a perceived social disadvantage related to childhood and adult short stature, is here to stay'

than half a standard deviation, treatment may be continued under supervision. If the response is poor, rhGH therapy should be stopped and the approach to management reconsidered.⁸

CONCLUSIONS

Management of ISS divides opinions. In countries following FDA guidelines, rhGH is prescribed and reimbursement is largely from insurance companies. In countries following EMA legislation, rhGH is prescribed sparingly, as national healthcare authorities use their resources for other priorities. Both the over-liberal and the over-restrictive extremes of rhGH prescription are inadvisable. Some ISS children with auxological evidence of true growth failure deserve a chance to respond. In contrast, many children from healthy short families are unlikely to benefit from rhGH. Every child needs individual assessment. Short stature per se is not an illness and 'average' is not the definition of 'normality'. Studies may show statistical differences compared with untreated subjects, but a statistical difference does not necessarily translate into clinical benefit.⁹

MARTIN O SAVAGE

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AN AGEING POPULATION, THE NATURE OF HEALTHCARE AND OUR NEED TO ADAPT

WRITTEN BY DAVID OLIVER

When the National Health Service was created in 1948, life expectancy at birth in England was 66 years for men and 71 for women. Nearly half the population died before they reached 65. The corresponding figure now is around 14%, with average expectancy around 20 years at age 65. Projections for 2030 are for a 50% increase in the number of over-65s and a 100% increase in over-85s – the fastest growing demographic. English men having their 65th birthday in 2030 can expect to live on average until 88 and women 91.

These compelling figures do have implications for the health and care workforce, dependency ratios (between those in paid employment and those not) and for retirement age, which we mustn't duck. But instead of a sensationalist narrative driving ageist attitudes through phrases like 'grey tsunami' and 'ticking time-bomb', ageing isn't all doom and gloom, but a cause for celebration.

WHY WE SHOULD CELEBRATE

First, this progress represents a victory for society through better nutrition, housing, hygiene, wealth and workplace safety. Secondly, it's a victory for modern healthcare, with death rates in all age groups from common killers (cancer excepted) all reducing throughout the past 50 years. Thirdly, it means we all have a higher chance of a long and active life. Fourthly, despite prevalent problems such as social isolation, in population studies, most over-75s self-report relatively good health, well-being and happiness – despite media stereotypes of 'the elderly' routinely beset by misery. Even the economic catastrophising is debatable. Economies grow, retirement age can increase and those over 65 probably make a net economic contribution through their roles as unpaid carers, grandparents and volunteers, and through spending and continued paid employment.

Although the population over 65 is, if anything, becoming healthier, with a possible reduction or delayed onset of morbidity, ageing inevitably means a higher overall number of older people living in poor health. There are still major inequalities in absolute and healthy life expectancy at 65, with around half of all poor health in older age potentially preventable through lifestyle across the life course.

IDENTIFYING NEEDS OF OLDER PEOPLE

With increasing age, people live with multiple long term conditions (those over 75 have three or more on average – though not always 'life-limiting', explaining the apparent paradox of high self-reported well-being). These, in turn, can lead to prescription of multiple medications, despite the fact that most clinical trials exclude older people with multiple co-morbidities and that clinical guidelines and pay for performance incentives focus on single conditions. Inappropriate or hazardous polypharmacy can lead to side effects, drug-drug or drug-disease interactions and poor adherence.

Dementia already affects around 800,000 people in England, with the number projected to double in the next 20 years. Mobility problems, hearing and visual impairment are increasingly prevalent in older age, as is frailty syndrome.

Frailty hasn't traditionally been discussed in plans and strategies around long term conditions, but it needs to be, as the British Geriatrics Society has set out in the recent 'Fit for Frailty' resource. People with frailty tend to fatigue more easily, have slower walking speed, reduced muscle strength and reduced functional reserve. A relatively small event such as infection, drug side effects or metabolic disturbance can cause rapid decompensation in people who are frail. They tend to present to health and care systems with non-textbook symptoms, falls, immobility,



Ten components of care for older people. From Oliver et al. 2014 Making Our Health and Care Systems Fit for an Ageing Population. London: The Kings Fund.

incontinence, acute confusion (delirium) and fluctuating disability. Frailty accounts for a big proportion of acute hospital activity, nursing home residents and users of community intermediate care services. But non-geriatricians are poorly trained in its recognition or in the skilled comprehensive geriatric assessment required to address it. All of these problems tend to travel with an older person, even if they are using health services for another reason, but require a change of approach when dealing with them.

CHALLENGES FOR CHANGE

With health and care systems under increasing financial strain, we can't solve pressing problems without addressing the care of older people. They account for proportionately the biggest spend, the biggest activity, the biggest unwarranted variation, the group most likely to suffer from poorly co-ordinated care and at inefficient interfaces and handoffs between agencies. Improve care for older people with complex needs and we can help improve it for all.

But we need radically to change our priorities and approach away from one designed for a population who died far younger or to deal with single conditions or episodic disease. Instead we need a focus on:

- prevention across the life course
- ensuring that when older people start to become frail or unwell

we maintain their independence, connections and ability to remain at home

- more continuity and 'person-centred co-ordinated care' for people living with frailty, dementia and multiple complex co-morbidities and based around them as individuals rather than single disease entities
- support for carers (there are around six million in the UK, many of whom are older people themselves)
- better collaboration and integrated working between hospital, primary and community care and social care (including the need for far more responsive rehab and support services outside hospital or better healthcare for nursing home residents).

Most importantly our politicians, national and local system and service leaders, educators, regulators, priority setters, research funders and universities, and crucially people training for and entering the caring professions, need to realise that, in the 21st century, older people are no longer a minority – the last to be considered – but are the core customers of our services.

Care and support for them will be the job of most of us, and we need to make our health and care systems age-proof and fit for purpose.

Those graduating in 2015 will have trained with the youngest group of patients and clients or research participants they are ever likely to work with. And older people are 'us' or our parents in the future, and our own relatives right now. Even older people don't like to see themselves as old and tend to distance themselves from ageing, but mass denial won't help us to achieve the transformation we need in modern services. It's time to get with the programme.

DAVID OLIVER

David Oliver is President of the British Geriatrics Society and Senior Visiting Fellow at The King's Fund, an independent charity working to improve health and healthcare in England. He is also Visiting Professor of Medicine for Older People, City University, London, and Consultant in Geriatrics and General Medicine, Royal Berkshire NHS Foundation Trust.

FURTHER READING

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A VIEW FROM THE LABORATORY – 40 YEARS ON

Dear Sir,

Congratulations on the recent 'history of endocrinology' issue of *The Endocrinologist* (issue 115), with contributions by so many cognoscenti and emeriti – a veritable arousal of endocrinologists! It complements nicely the personal interviews published in previous issues with senior endocrinologists and scientists who were reared in a 'golden' age of the specialty.

With the passing of time we all have our own notions of what made it 'golden'. My own perspective was as a chemical endocrinologist/chemical pathologist concerned mainly with measuring hormones. The laboratory was central to the rapid evolution of clinical endocrinology in the 1970s – in particular the development of radioimmunoassays (RIAs) to measure circulating hormone levels with high sensitivity, and specificity. At St Bartholomew's Hospital, where I started as a lecturer in 1968, great credit should go to John Landon, newly appointed Professor of Chemical Pathology, for setting up an endocrine laboratory where young clinicians and scientists worked together, often at closer quarters than would be allowed under present health and safety regulations! At that time, the hospital endocrine menu offered little more than the Mattingly method for fluorogenic corticosteroids and a non-specific method for glucose. The assessment of thyroid function by protein-bound iodine was just an aspiration.

The starting mantra for measuring hormones was 'first make your reagents', as few were available commercially – and those that were available were of dubious quality. However, this DIY approach had

the advantage that we became fully aware of the potential pitfalls of the assays and their interpretation. It took me about a year of trying to measure adrenocorticotrophin before I was able to confidently distinguish 'nothing' from 'something' to clinch a differential diagnosis of Cushing's syndrome.

The second point I would stress is that, in the early days of hormone RIAs, the need for accurate interpretation encouraged really effective collaboration between specialties. After I moved to the Royal Infirmary in Glasgow in the 1970s, turnaround times for most pituitary hormones became faster, dynamic tests for pituitary function were developed, and transphenoidal surgery for microprolactinomas was pioneered by Graham Teasdale at the Southern General Hospital.

We set up interdisciplinary sessions to review all the hormone results from each patient with endocrinologists, neurosurgeons, chemical pathologists and biochemists from the main teaching hospitals across the city. These proved efficient, educational and motivational. It seems to have taken over a decade before this excellent practice was taken up by London centres. In an era before continuing professional development, this form of collaboration between specialties remains with me as the best way to foster the contributions of all involved.

Yours faithfully,

JOHN RATCLIFFE

Emeritus Professor of Chemical Pathology, University of Manchester, and of Clinical Chemistry, University of Birmingham

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LETTER TO THE EDITOR

OPINION



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ENDOCRINE REJUVENATION: IS THE ROLLERCOASTER DESTINED TO END ON A HIGH?

WRITTEN BY AUBREY DE GREY



As all endocrinologists are aware, the field has been immensely influenced since its earliest days by the idea that hormones might constitute the elixir of life. Moreover, this influence has always been massively double-edged: hope and despair have alternated rapidly, as has the associated reputation of the more prominent proponents of 'this or that' therapy. Is this to be the field's eternal fate?

Here, let me argue for the optimistic conclusion that our progress – both in our understanding of the role of hormonal changes with age and in our ability to prevent or reverse those changes – is, by now, set on a clear trajectory of overall success. In short, the light at the end of the endocrinology-of-ageing tunnel is now clearly visible.

BETTER KNOWLEDGE

There have been few changes in recent times to the core tools with which we discover what molecules are present in the circulation, how their levels are regulated, and how they in turn regulate other factors. However, one tool with a long history has been conspicuously revived in the past decade, following many years of neglect. This is parabiosis, and its close cousin plasma exchange.

Heterochronic parabiosis, i.e. the conjoining of the circulations of a young and an old animal, is of course only the first step in this journey. It has obvious limitations in terms of clinical applicability, and even in interpretation in the laboratory, in view of the stress associated with the required surgery and the potential for immuno-incompatibility. But, in spite of this, researchers have been able to use the technique to identify not only a range of rejuvenating effects on the old parabiont, but also some of the circulating factors that appear to confer those effects.

So, now what? The key to better, more systematic discovery of key factors is the ability to add and/or remove them en route from one animal to the other, and above all to reduce the stress on the animals sufficiently to permit long term experiments that can reveal gradual effects. Devices of increasing sophistication are in development that promise exactly this.

REJUVENATING THE ENDS OF THE PIPELINE

The circulation is, after all, simply a conduit: it is not the problem, it is the messenger of the problem. As such, the design of therapies must always incorporate the possibility of direct interventions to rejuvenate both the organs that are influencing the levels of circulating factors and those whose responsiveness to such factors is changing. Regarding the latter, and to take the best known example of insulin resistance, it remains important to manipulate

skeletal muscle directly so as to restore glucose intake capacity. Measures to induce uncoupled respiration are of particular promise in this regard. Equivalent interventions in other organs are a high priority.

The fundamental limitation of today's hormone replacement therapy is the schedule of release. Timed release is better than a bolus, but ultimately the need is for release to be regulated in response to those same factors that regulate it naturally. Insulin is again at the forefront of such work, and the pace of progress gives ample cause for optimism that such technology will soon be diversified for use in relation to other hormones. This remains a big engineering challenge. Not least, we must bear in mind that the highly localised circuitry of some key components of the neuroendocrine network poses daunting technical obstacles to the development of truly comprehensive maintenance of endocrine stability, in the face of ageing of glands and receptor tissues. But the time to address that challenge is now.

THE END-GAME: LEAVING THE CIRCULATION BE

I alluded above to rejuvenation of tissues that respond to hormones; what about those that secrete them? While artificial devices can in principle insulate one from the other, by buffering hormone levels with ever-increasing fidelity, the alternative of simply rejuvenating the natural source may prove easier and superior. Full blown success in that approach would remove any need to monitor, let alone manipulate, circulating factors.

Our options are hearteningly diverse. To take the pancreas as an example: we can rejuvenate at the molecular level, such as by removing islet amyloid via the same approaches that have already succeeded against amyloid beta in the brain. We can rejuvenate at the cellular level, by restoring islet cells and insulin production via stem cell therapy. And we can also rejuvenate at the whole organ level, by transplanting a tissue-engineered pancreas. All such approaches are eminently foreseeable and practical at this point.

CONCLUSION: THE FUTURE IS BRIGHT

The endocrinology of ageing has traversed a rocky road. But, so what? So do most pioneering fields, and especially those with such promise for impact on humanity. But today, our technological versatility and our breadth of knowledge – and the pace at which both are increasing – leave no reasonable doubt that we are on course to bring this aspect of ageing under thorough control soon.

AUBREY DE GREY

Chief Science Officer, SENS Research Foundation, USA

Twitter: @aubreydegrey





A THIRD DIMENSION

FROM OUR SCIENCE COMMITTEE CORRESPONDENT

Cambridge has never found it hard to get steady work as a supporting actor. Blessed with striking good looks and strong connections to media movers and shakers, the colleges up and down the Cam have served as a reassuring backdrop in many high profile films. From the Walter Raleigh cloak-over-a-puddle scene in Cate Blanchett's *Elizabeth: The Golden Age* to the May Ball in Eddie Redmayne's triumphant *The Theory of Everything*, the late gothic college courts can be relied upon to do the business.

One recent, but less high profile, film that also frames some of the action within a college is *X+Y*. Without wishing to throw in plot spoilers, this is the story of an awkward and troubled prodigy evolving into a happier and more fulfilled person through a personal journey of discovery on the International Mathematical Olympiad circuit. This might sound mawkish and hackneyed to a hardened and cynical scientific audience and, yes, there are hammy moments of cliché. However, I was caught off guard by this film, with the warmth of the characters and light touch of the adult leads winning me round. It made me laugh and cry and I came out at the end feeling happier and uplifted.

This no doubt says something unflattering about my wobbly psyche, but over and above that was the reminder of the emotional power –

good and bad – of problem-solving and pure thinking. Thought and emotion are not a disconnected duality. Being unable to carry other peoples' sensitivities, being unable to turn off intrusive and questioning thoughts, being out of synch with the world around, can be isolating and damaging. In contrast, having the ability to reside in a world of logic and reason can provide great solace in troubling times and serve a useful purpose to the wider world.

Even more, when science is good, the sheer beauty of the thing makes it laugh-out-loud fun. Remember the last time you saw or, even better, generated data that made you crackle and fizz with excitement, when the sum of the two-dimensional plot took on much more of a meaning than the component abscissae and ordinates? Such moments can make the world look different: colours are brighter, travel is less of a chore, meetings are more productive.

Go and look for a graph that makes you grin. Cut it out and stick it on the fridge – because science is better when you are smiling.

TONY COLL
Science Committee correspondent



FRESH FOCUS

FROM OUR CLINICAL COMMITTEE CORRESPONDENT

The Society for Endocrinology's Clinical Committee has always had a broad remit, including reviewing and endorsing clinical guidelines and affiliated events, identifying problems in pharmaceutical drug supply (who can forget recent issues in synacthen availability?) and supporting recruitment and training of clinicians in the specialty.

In 2014, Wiebke Arlt became Committee Chair, following Jayne Franklyn's retirement at the end of her busy term of office. As ever, a change in leadership has brought some changes to the Committee's direction. While retaining its broad remit and interest in guiding a variety of clinical issues, it currently has a particular focus on certain themes and proposed changes in its membership.

The Committee has three major tenets:

- clinical practice and governance
- clinical research and clinical education
- training and career development.

While all are equally important, recent problems in recruiting clinical trainees to higher specialist training in diabetes/endocrinology, along with looming changes in clinical training following the publication of the *Shape of Training* report in 2013, mean that issues surrounding education, training and development of potential clinical trainees are being given particular prominence. One achievement of the Committee in this area has been its role in developing the *Clinical Careers in Endocrinology* booklet. This is available for distribution to medical students and undifferentiated clinical trainees, and was unveiled at recent medical careers fairs held simultaneously in London and Glasgow.

The Committee also recently approved changes in its composition to improve efficiency and generate more effective debate. This will see a reduction in the number of elected full members over time (as terms of office expire) to 12. In addition, given the traditional close association between clinical endocrinology and research, there is an ambition to strengthen clinical academic representation. The Committee will, however, still retain a broad variety in its clinical membership, with ongoing representation of clinically and scientifically active members from both university and tertiary teaching centres as well as non-tertiary centres.

As a result of these changes, meetings are becoming more interactive and lively. Members now have volunteered (or been persuaded) to take on designated responsibilities that are associated with the Committee's major aims (for instance, one of my roles is liaison with *The Endocrinologist*).

So, the Clinical Committee is an exciting place to be. We encourage all Society members to contact us with any issues that you think might be relevant. We always welcome enquiries from practising clinicians regarding membership.

MARIE FREELY
Clinical Committee correspondent

To get in touch with the Clinical Committee, email members@endocrinology.org.

SPOTLIGHT ON SPRING 2015: FOCUS ON SOCIETY EVENTS



OBESITY UPDATE

12 January 2015, London

Total delegates: 90

Abstracts submitted: 27

Oral comms top prize:

Vidhya Jaha Girdar

Poster prizes: Vasileios Chortis,
George Dimitriadis, Christine May

'The Update provided a very good overview of a number of different aspects of managing obesity with great practical as well as educational components'

'It was excellent to hear about the research currently happening and the new ideas emerging about the physiology of obesity within medicine today'

100% would recommend Obesity Update to a friend or colleague

NEW FORMAT FOR 2015! ENDOCRINE NURSE UPDATE

16-17 March 2015, Birmingham

Total delegates: 54

For the first time, ENU featured six fantastic Clinical Update crossover lectures:

- Intervention strategies to achieve weight loss
- Practical management of anorexia
- Lifelong management of Turner syndrome
- Disorders of sex development
- Traumatic brain injury
- Nuclear imaging and therapy

'Both the nurse and combined sessions were really very informative, so great to take away specific knowledge to put into practice'

'All very interesting speakers, there was not one session I would not have chosen to go to'

ESE BASIC SCIENCE COURSE IN REPRODUCTIVE ENDOCRINOLOGY

18-20 February 2015, Edinburgh

Total delegates: 42

Abstracts submitted: 16

Oral comms top prize: Cheng Xu

Poster prizes: Thomas Chambers, Avi Lerner

'Great to see such a high standard of oral presentations by both the experts and younger members'

'The great ratio of faculty members to delegates allowed delegates not only to network with peers, but also with more established endocrinologists who were incredibly supportive and engaged throughout'

CLINICAL UPDATE

16-18 March 2015,
Birmingham

Total delegates: 152

Abstracts submitted: 56

Featuring this year's Clinical Endocrinology Trust Lecturer

Ashley Grossman (Oxford), discussing 'Where do pituitary tumours come from?'



'Workshops were clinical, practical and relevant and just an excellent chance to hear from approachable experts in the field and ask them questions'

'Very clinically relevant. Great for trainees as covers lots of the curriculum and a good opportunity to present cases and ask questions'

NATIONAL CLINICAL CASES MEETING

26 February 2015,
London

Total delegates: 97

Abstracts submitted: 44

Oral comms top prize:

Andrew Powlson

Poster prizes:

Vasileios Kusuma

Boregowda, Shona

Jacobsberg, Sam O'Toole

Particular congratulations are due to **Ada Teo**, who received the Royal Society of Medicine (RSM) oral prize for 'Unmasking of Conn's syndrome by pregnancy in a patient with somatic *CTNNB1* mutation', and also **Sarah Denny**, who received the RSM poster prize for 'Homeopathy in the treatment of hyperthyroidism'.

FIND MORE ONLINE

Get the latest Society events and training information at
www.endocrinology.org/meetings

EAT, SLEEP, WAKE, REPEAT! A DAY IN THE LIFE OF YOUR HORMONES

WRITTEN BY FIONA DOCHERTY



Ever wondered how you wake up in the morning? Or fall asleep at night? Or know when you're full after eating? These are the questions that we set out to answer during our latest public engagement programme.

We kicked off our 2015 calendar of public engagement events with the Big Bang Fair – the biggest science and engineering education event in the UK. The Fair attracts 75,000 visitors over 4 days, and this year it took place at Birmingham's NEC. Eight Society for Endocrinology members, most of whom were PhD students from the

Where? – Big Bang Fair, Birmingham NEC

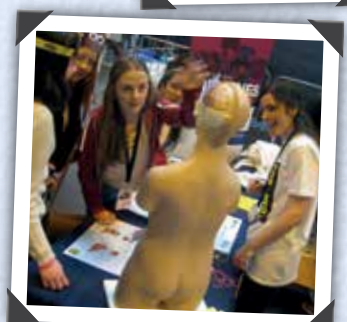
Size? – 75,000 attendees

Duration? – 4 days

'Eat, Sleep, Wake, Repeat' visitors? – 3,500

Audience? – 7- to 19-year-olds plus family groups

ADMIT ONE



University of Birmingham, volunteered to help us run the event.

Visitors who participated followed a day in the life of their endocrine system and discovered how their hormones work together to keep their body clocks on time. We had activities that allowed visitors to make their own body clocks, map the path of hunger hormones and carry out 'blood' glucose testing.

The event was a great success. We received a staggering 3,500 visitors at a variety of learning stages, including primary school



and secondary school pupils, as well as some teachers and parents.

In fact, everything went so well that we've decide to take 'Eat, Sleep, Wake, Repeat!' on the road. Next stop: Cheltenham Science Festival!

FIONA DOCHERTY
Communications Executive,
Society for Endocrinology

Quotes from our volunteers

'I have a passion for science which I want share with younger children to get them inspired'

VICKI POOLE, PhD STUDENT

'I usually find that I communicate my research to my peers so it's nice to explore other ways of getting concepts across'

LORNA GILLIGAN, PhD STUDENT

'I've never done any public engagement before and felt it was time to give something back. I'm used to teaching 18- to 25-year-olds. You have to find a different way to explain the same things in a much simpler way ... it's challenging but very rewarding'

**DEREK RENSHAW, PROFESSOR OF APPLIED BIOLOGICAL SCIENCES,
COVENTRY UNIVERSITY, AND SOCIETY FOR ENDOCRINOLOGY SCIENCE
COMMITTEE MEMBER**





 2 – 4 November
EDINBURGH

BIGGER & BETTER: SOCIETY FOR ENDOCRINOLOGY BES 2015

The EICC, Edinburgh, UK.
2-4 November 2015

You're sure to enjoy this year's SfE BES conference, with novel initiatives to help you in your professional career, and an exciting new 3-day format jam-packed with clinical and scientific discoveries.

SfE BES 2015 KEY DATES

Abstract Deadline:
15 June 2015

Early Bird Registration:
21 September 2015

Get the latest info:
#SFEBS15

LOOKING FORWARD TO 'FUTURES'

Open to all, but with specialist trainees, medical students, undifferentiated trainees and biological sciences graduates in mind, our new 'Futures' series comprises tailored sessions providing advice for the next step in your career. You will enjoy first-hand testimonials and panel discussions from senior colleagues and peers, covering practical tips – come and be inspired!

FUTURES 1: BRANCHING OUT WITH ENDOCRINOLOGY

Making the most of your degree(s): matching your skills to academic careers

Monday 2 November 12.15–13.00
Chairs: Ruth Andrew (Edinburgh) & Samantha Mirczuk (London)

Definitely attend if... you're a bioscience student or graduate

FUTURES 2: OVERCOMING THE CONSULTANCY HURDLE

Shaping the future of endocrinology and diabetes

Monday 2 November 12.15–13.00
Chairs: Miles Levy (Leicester) & Sheba Jarvis (London)

Definitely attend if... you're a trainee (specialist or undifferentiated)

FUTURES 3: WHY ENDOCRINOLOGY AND DIABETES?

The must-see session for all medical students and undifferentiated trainees

Monday 2 November 20.00–20.45
Chairs: Karim Meeran (London) & Dominic Cavlan (London)

Definitely attend if... you're a medical student or undifferentiated trainee

SEEKING OUT 'SKILLS'

Communicating science matters – to raise awareness of your field shape public opinion or inform lifestyle choices. This year's 'Skills' series looks at how the media works, how to get your work to a broad audience, and ways of tackling sensitive issues such as animals in research.

SKILLS 1: WORKING WITH THE MEDIA

Monday 2 November 10.30–12.00
Chair: Saffron Whitehead (London)

SKILLS 2: EARLY CAREER SYMPOSIUM: EFFECTIVE COMMUNICATION – GET INVOLVED, GET ENGAGED!

Successfully conveying science to the general public

Tuesday 3 November 10.30–12.00
Chairs: Anna Mitchell (Newcastle upon Tyne) & Kate Lines (Oxford)

MAKE YOUR WORK PART OF SfE BES 2015!

Don't miss your opportunity to present your research at the largest UK endocrine conference. Submit an abstract today to be eligible for over 20 awards and prizes at SfE BES 2015.

ABSTRACT DEADLINE:
MONDAY 15 JUNE 2015 (23.59 BST)

SUBMIT YOUR ABSTRACT ONLINE:
WWW.ENDOCRINOLOGY.ORG/MEETINGS/2015/SFEBES2015

A YEAR IN REVIEW: TYPE 2 DIABETES

It has been an exciting time for diabetes research. SfE BES 2015 will host an inspiring leader in diabetes research, providing you with a comprehensive review of the worldwide progress in type 2 diabetes.

DON'T MISS THE ENDOCRINE POST!

The Society for Endocrinology's brand new blog

To hear more on Society initiatives and updates from the world of hormones, visit <http://endocrinologyblog.org>

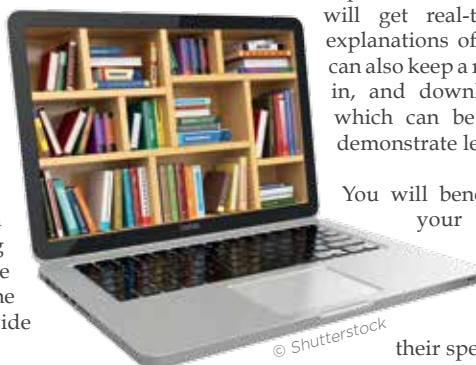
NEW! JOURNAL-BASED LEARNING FROM BIOSCIENTIFICA

WRITTEN BY KATHERINE SINGLE



Bioscientifica, the Society for Endocrinology's trading company, provide publishing, association management and events services to the biomedical community. All of the company's profits are distributed back to its partner societies.

Bioscientifica publish five of the Society for Endocrinology's official journals, so we are always on the lookout for new ways to enhance members' reading and learning experiences, and to support endocrine education. That's why we have launched an online journal-based learning programme, which will provide a new learning experience for all our readers.



Selected articles in Bioscientifica's journals now feature questions written in collaboration with experts in endocrinology and related disciplines. When you complete learning activities, you will get real-time scores, including comprehensive explanations of the correct and incorrect answers. You can also keep a record of the activities that you participate in, and download formal certificates of completion, which can be uploaded to your NHS ePortfolio to demonstrate learning.

You will benefit from this resource at any stage in your career. The programme supports the education of clinicians-in-training and early career scientists, and will keep senior healthcare professionals up to date with the latest knowledge in their specialty.

Current journal-based learning topics

<i>Journal of Endocrinology</i>	Glucocorticoid treatment and endocrine pancreas function
<i>Journal of Molecular Endocrinology</i>	Beta-cell regeneration and differentiation: how close are we to the 'holy grail'?
<i>Endocrine-Related Cancer</i>	Current controversies in initial post-surgical radioiodine therapy for thyroid cancer
<i>European Journal of Endocrinology</i>	Mechanisms in endocrinology: thyroid and polycystic ovary syndrome
<i>Endocrine Connections</i>	The heart as an endocrine organ

This interactive resource has been developed with Digitec, who have a proven record of delivering e-learning courses for associations and non-profit organisations, including the International Society on Thrombosis and Haemostasis and the Association for Professionals in Infection Control and Epidemiology.

Bioscientifica's journal-based learning programme is completely free to use. To participate, all you need to do is register at <http://bioscientifica.knowledgedirectweb.com>.

KATHERINE SINGLE
Corporate Marketing Manager,
Society for Endocrinology and Bioscientifica

GENERAL NEWS OBITUARY

STELLA AMEYO ADADEVOH

HOW A UK-TRAINED ENDOCRINOLOGIST SAVED NIGERIA FROM EBOLA



Dr Stella Ameyo Adadevoh was an endocrinologist who helped avoid a devastating outbreak of Ebola in Nigeria. Despite having limited safety equipment and lacking the appropriate training, Dr Adadevoh took swift and firm action by diagnosing Nigeria's index patient, a move that saved countless Nigerian lives, at the cost of her own.

A fellow in endocrinology at Hammersmith Hospital, London, between 1991 and 1993, Dr Adadevoh treated Liberian civil servant Patrick Sawyer after he was found having collapsed in Lagos airport. Mr Sawyer claimed he had a bad case of malaria and avoided telling staff that his sister had died of Ebola 2 weeks previously. Dr Adadevoh made a sharp-eyed diagnosis of the disease, kept him quarantined and alerted the health authorities. Despite the patient's aggressive threats to staff and political pressure from the Liberian ambassador,

Dr Adadevoh stood her ground and refused to release Mr Sawyer.

Within 3 weeks of Mr Sawyer's death, Dr Adadevoh was rushed to hospital and diagnosed with Ebola. She died aged 57 on 19 August 2014, leaving a son and husband. The Nigerian and British press have heralded Dr Adadevoh as a heroine, and the Nigerian parliament has moved to rename the infectious diseases hospital – where she died – in her memory. Dr Adadevoh's son has set up a trust to honour his mother.

The Society extends its condolences to Dr Adadevoh's family. For more information about the health trust for Dr Stella Adadevoh, visit www.drastatrast.org.

OMAR JAMSHED
Communications Executive, Society for Endocrinology

EXPANDED COMPETENCY FRAMEWORK REACHES EVEN WIDER AUDIENCE

WRITTEN BY SHASHANA SHALET

The second edition of the highly successful *Competency Framework for Adult Endocrine Nursing* has now been launched and, for the first time, the full framework has been published in *Endocrine Connections*.¹ Publication on the internet in this way enables us to inform a wider audience of the document's existence, due to its open access format.

Previous promotion of the framework at the meetings of the Society for Endocrinology in the UK and The Endocrine Society in the USA, as well as at the European Congress of Endocrinology, has enabled the document's authors to reach both a medical and a nursing audience. Active promotion both by the panel of endocrine specialist nurses who compiled the framework and by the Society for Endocrinology has also increased its readership, with translation of the framework into a further six European languages to be completed shortly, kindly facilitated by the European Society of Endocrinology.

The first edition², published in 2013, included the topics:

- Acromegaly
- Cushing's syndrome
- Endocrine dynamic function testing
- Growth hormone deficiency
- Hypogonadism
- Hypopituitarism
- Steroid replacement therapy for disorders of the pituitary and adrenal glands
- Thyroid disease
- Transition

This first edition provided a clear structure against which managers could benchmark current practice, and that could also enable discussions around personal career progression and facilitate examination of wider service development through new nurse-led clinics.

The second edition includes four additional topics:

- Benign adrenal tumours
- Hypo- and hyperparathyroidism
- Osteoporosis
- Polycystic ovary syndrome

The development of the competencies has taken much thought and time on the part of a panel of endocrine specialist nurses from across the UK, who between them have a vast number of years of endocrine experience. Their original remit was to provide a way to standardise the role of the endocrine specialist nurse, to promote patient safety and to provide clear goals for career progression.

The document is currently in use in my department as a way of training members of staff who are new to endocrinology by providing a clear framework to assess their knowledge and understanding. It highlights any knowledge gaps whilst demonstrating how much they have learned as a motivational tool. This framework will enable both individual and organisational development which will benefit the nursing team

and endocrine service as a whole, whilst ultimately being able to offer consistently high standards of patient care across the UK.

SHASHANA SHALET
Endocrine Advanced Nurse Practitioner,
Salford Royal NHS Foundation Trust

REFERENCES

1. Kieffer V et al. 2015 *Endocrine Connections* 4 W1–W17.
2. Kieffer V et al. 2013 *Competency Framework for Adult Endocrine Nursing*. Bristol, UK: Society for Endocrinology.

DOWNLOAD NOW!

You can download the second edition of the *Competency Framework for Adult Endocrine Nursing* free of charge from *Endocrine Connections* at <http://bit.ly/1ICxpWG>. Both the first and second editions are also available via www.endocrinology.org/endocrinurse/competencyFramework.html.

LISA SHEPHERD

NURSE COMMITTEE CHAIR



In this issue, Shashana's article highlights the successful publication of the second edition of the *Competency Framework for Adult Endocrine Nursing*. The framework has met with not only national but also international success. Its promotion at recent high profile endocrinology meetings will be followed by its translation into other languages, and these versions are to be launched imminently. The framework can be utilised not only to benchmark current practice, but also to assist career progression and identify training needs.

The launch this year of 'revalidation', proposed by the Nursing and Midwifery Council (NMC) (www.nmc.org.uk/standards/revalidation), highlights the importance of up to date practice and professional development. The NMC stipulates that, as nurses, we need to develop new skills, keep informed about standards and understand the changing needs both of the public we serve and of our fellow healthcare professionals. Revalidation will give the public, employers and fellow professionals greater confidence that nurses and midwives are up to date with their practice.

Evidence to support your revalidation can be secured through attendance and reflection of learning at Society for Endocrinology conferences and use of the *Competency Framework for Adult Endocrine Nursing* in practice.

Finally, it was good to see so many new (and dare I say 'old') faces at the new combined format Endocrine Nurse Update/Clinical Update in March. What better way to continue updating your practice, knowledge and skills than by attending SfE BES 2015 in November in Edinburgh! Don't forget the abstract submission deadline on 15 June, and to apply for your Travel Grant by 15 July. See www.endocrinology.org for further details.

LISA SHEPHERD

OUT OF THE COMFORT ZONE? WORKING ABROAD

WRITTEN BY JOHN POOLEY

It's not the most comfortable feeling, being asked to remain behind following a lab meeting. Thankfully I was not in trouble. My boss was curious regarding my post-PhD plans and revealed he might have something I would be interested in. There was a catch however ... the position wasn't here, in the nice safe and comfortable environment I knew, but thousands of miles away across the Atlantic.

While I was presented with the opportunity to work abroad, there are many reasons the aspiring researcher might deliberately seek out such an adventure.

PUSHING THE BOUNDARIES

Going abroad should certainly offer something that is not currently accessible to you. I found new technologies and methodologies that allowed me to explore innovative research goals, funding to implement novel but risky ideas, and some exceptionally talented people to learn from. I worked in a laboratory I admired for pushing the boundaries of my thinking, I absorbed new ideas and perspectives in my own field and beyond, and I tackled an interesting problem from new angles that I could not have attempted at home. I set out alone to prove my worth as an independent scientist, establishing my own priorities and research questions and forming new collaborations and connections.

There may be other perks depending on where you are: hot and bright summers, beautiful snowy winters, travels to 'the wonders of the world', the joys of taking part in festivals and events we simply don't have, new sports and activities, and the learning of different languages or expressions.

CLIMBING THE LEARNING CURVE

It is unfortunately far from easy to build a project from scratch in a foreign land. I had to stand on my own feet, procure what I needed and produce results. My host, with

no background in what I was doing, was generally limited in the advice he could give, and problems that developed were mine to solve. Colleagues do their best to help 'the new guy', but may be too busy with their own experiments to adequately demonstrate procedures and methods.

I found the experience a steep uphill learning curve, walked largely alone. Distance from family and friends does hurt, and is not for everyone. But Mum and Dad were unexpectedly on-board with the idea, planning their summer holidays at my new location before I even left. It's actually you that feels the isolation most, particularly in the first months, as you struggle to develop new friendships.

'Moving away from everything you were familiar with was, in fact, the point ... Familiarity is a comfortable misfortune'

But to aspiring adventurers, I describe a rite of passage, not a lasting sentence. Moving away from everything you knew and were familiar with was, in fact, the point – and it takes time to re-build. Familiarity is a comfortable misfortune.

REFRESHING YOUR PERSPECTIVE

On that last point – going abroad was an opportunity to hit life's reset button, so remaking a new life that I was happy with. My familiar life had stalled before I got on that plane. I wasn't happy with my work-life balance, what I spent my time doing, and the bulk of people (close friends and many colleagues aside) I was spending it with. Scientifically, I'd spent years doing the same things and was perhaps bored, certainly run down, and in need of fresh challenges to recover my passion for research.

Overseas, I threw myself at new activities and new research goals, and built new relationships without preconceived expectations. I immersed myself in a different culture revealing new perspectives on the UK's successes and failures.



©John Pooley

Now having returned to the UK, I'm tasked with completing lines of investigation while transferring methodological approaches learned overseas to this country. Working abroad was an exceptional experience that benefited my career and personal life in equal measure. By demonstrating that you'll take opportunities to empower yourself, reach

beyond your comfort zone and take in new ideas, you also increase your employability.

If you are too comfortable in your science currently, this sort of shake-up might be for you. It's not, of course, until you look back after such an experience that you appreciate the difference a period abroad can make; and I haven't found an environment more conducive to this process than the long flight home. When the airline pilot announces the expected weather on your approach into the UK (overcast with light rain), you may even begin considering where your next research project could take both you and your career.

JOHN POOLEY

John Pooley is a BBSRC-funded Postdoctoral Research Assistant at the Henry Wellcome Laboratories for Integrated Neuroscience and Endocrinology at the University of Bristol. His visit to the National Institutes of Health (NIH; Bethesda, MD, USA) was supported by the Neuroendocrine Charitable Trust, a BBSRC International Scientific Interchange Scheme Award, a Society for Endocrinology Early Career Grant and the Intramural Research Program of the NIH.



©John Pooley

CALLING ALL STUDENT AMBASSADORS!

Are you passionate about endocrinology?

Do you want to have an active impact on your profession?

If so, take your place as a Society for Endocrinology Student Ambassador...

From 2015, Society for Endocrinology Student Members and Scientist-in-Training Members who are PhD students can become Dedicated Student Ambassadors. Valuable and rewarding, becoming a Student Ambassador will place you at the very centre of the field of endocrinology. As an Ambassador, you will be actively involved in providing a vital link between fellow students, your institution, the Society and the endocrine community.

As well as providing an essential voice for fellow students, Ambassadors will cultivate important, transferable skills while taking an active role in the Society's mission to advance endocrinology.

As an Ambassador, you will get involved in many different activities including, amongst others:

- Promoting the Society's work to fellow students within your institution
- Being a voice for the student community, attending focus groups and advising on Society Student Member policy and activities
- Providing thought-provoking articles for the new Student Ambassador area of the Society's website and for *The Endocrinologist*
- Setting up and hosting an Endocrine Club from your institution. Alternatively, if you are already part of a local Endocrine Club or Society, we will help you connect with endocrine clubs at different institutions.

The scheme will give you, the endocrine professionals of tomorrow, the chance to get actively involved in the wider world of endocrinology, to expand your CVs and to speak for your institution and fellow students.

All Student Members and Scientist-in-Training Members who are PhD students are encouraged to apply to become Ambassadors. Two or three representatives will be appointed at each university/institution, with the aim to achieve a balance between medics and scientists. The initial term will be up to 2 years.

Email members@endocrinology.org today to find out more!

IN THE NEXT ISSUE OF THE ENDOCRINOLOGIST... MEET OUR FIRST STUDENT AMBASSADORS

Parisut and Rakhee, our first Society for Endocrinology Student Ambassadors, are currently medical students at the University of Cambridge. In 2014 they set up a hugely successful



Parisut Kimkool
CUES President
2013-2014

University-recognised endocrinology society (Cambridge University Endocrinology Society, CUES; <http://cuendosoc.soc.srcf.net>), providing a vital space for like-minded students to explore their common interest, supplement their knowledge and discover a platform to discuss and debate current endocrine concepts.

'This experience has been invaluable and we would highly recommend other students to take up the rewarding role of bridging the gap between students and specialists. We leapt in and we hope you will too!'



Rakhee Vaja
CUES Secretary
2013-2014



Two Society Members, Saira Hameed and Amir Sam, attended the Imperial College Medical Careers Fair on the Society's behalf earlier this year, with the aim of encouraging medical students into the Endocrinology and Diabetes specialty.

With our newly produced *Clinical Careers in Endocrinology & Diabetes* booklet close at hand, the event was a great success and they were inundated with people signing up to find out more about careers in endocrinology.

If you would like to help with our careers work and inspire the endocrinologists of the future, email us at careers@endocrinology.org or visit www.endocrinology.org/careers to find out more and to download a free copy of our Clinical Careers booklet.

WOMEN IN ENDOCRINOLOGY: THE VIEW FROM THE GLASS CEILING

WRITTEN BY KAREN CHAPMAN



On 13 May 2014, three women stood in Manchester's Museum of Science and Industry to mark an historic event. What made this occasion so remarkable were the positions these three women occupied: the Presidencies of the Royal Society of Chemistry, the Institute of Physics and the Society of Biology. They were Professor Lesley Yellowlees CBE FRSE FRSC, Dr Frances Saunders CB FREng FInstP and Dame Nancy Rothwell FSB FRS respectively.

For the first time, all three Presidents were women (Professor Rothwell has since handed her role to another hugely impressive woman, Professor Dame Jean Thomas). The three women issued a joint statement including the following comment.

'At school, girls out-perform boys in all three sciences at GCSE. However, ... if you survey along the career ladder, women progressively disappear from view. Across the UK many young women do not believe a career in science-based roles is available to them ... Government and the scientific community must work together to provide the support needed to allow women to reach the top in science.'

EXAMINING THE EVIDENCE

I 'grew up' as a scientist thinking that the playing field was level as regards gender. I never encountered overt gender discrimination (though I was once asked if I intended to start a family – would my husband have been asked the same question?). However, gender bias clearly exists. Look at the data.

The Royal Society was founded in 1660, yet the first female Fellows were only appointed in 1945. Of the roughly 1,600 Fellows and Foreign Members alive today, only around 6% are women. Although this figure is improving, still far more men are appointed as new Fellows of the Royal Society than women.

The bias starts early. Following a recent paper in *Current Biology*,¹ the magazine *Science* developed a widget² that predicts an individual's chance of becoming a principal investigator (defined as occupying the last author position on publications). The number one predictor of success is to be male.

Over the last 3 years, the success rate for women applying for large grants from the UK Research Councils was 24%, whereas for men it was 38%.³ To 2014, only 18% of Wellcome Trust New Investigator Awardees were female, and only 16% of Senior Investigator Awardees. In the most recent round, only 4.6% of Royal Society University Research Fellows were female. Shocking, isn't it?

CONSIDERING THE CAUSE

Although some of these data include the physical sciences, women remain under-represented in biomedical science. It's often assumed that women's careers fall behind those of their male colleagues because women do the majority of childcare. However, look at the data more closely: a report from the Royal Society of Edinburgh⁴ found that although single women without children are only 2% less likely than married men with children to get a tenure track position, they are 23% less likely to achieve tenure than men. Why is this the case when we, as scientists, pride ourselves on our unbiased nature and objective approach?

Whilst few of us are guilty of conscious discrimination, we all show unconscious bias: our implicit people preferences, formed by our socialisation, our experiences, and our exposure to others' views. In a report entitled *Women in Scientific Careers*,⁵ the House of Commons Science and Technology Committee recommended that diversity and equality training, including unconscious bias training, should be mandatory for all members of recruitment and promotion panels for science, technology, engineering and mathematics (STEM) jobs in higher education institutions, and all line managers and supervisors of staff. It is probably the single most important thing that will make a difference.

SEEKING SOLUTIONS

It's all very well complaining. What are we doing? Many readers of *The Endocrinologist* will have come across the Athena SWAN Charter. Dame Sally Davies' now famous letter⁶ (if you haven't read it, you should!) coupled eligibility for National Institute for Health Research funding to an Athena SWAN Silver Award to medical schools in England and Wales (SWAN is an acronym for Scientific Women's Academic Network).

This kick-started a scramble (and not just in medical schools) to implement actions to promote gender equality in STEM subjects (now including medicine too) across the UK. Some initiatives are female-specific (e.g. around maternity leave and support). Others though, will improve equality of opportunity for everyone.

'Poor working practices discriminate against women, but good working practices benefit all.'

It has been said that 'poor working practices discriminate against women, but good working practices benefit all'. Good practice includes mandatory training in equality and diversity and unconscious bias, provision of mentoring, and the adoption of fair and transparent processes, for example in promotion. It is crucial to challenge the long-standing system of patronage that pervades academia and particularly medicine.

Role models are important: 'If they can do it, then maybe so can I!' We have our own inspirational examples in the Society for Endocrinology, where Julia Buckingham, Jayne Franklyn, Wiebke Arlt, Saffron Whitehead and many others all hold, or have held, key positions.

These women, as well as Presidents Saunders, Rothwell and Yellowlees and their like, are shaping change and inspiring the next generation, to improve diversity and equal opportunities for us all. Go for it!

KAREN CHAPMAN

Professor of Molecular Endocrinology, University of Edinburgh and,
Chair of the Society for Endocrinology Science Committee

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WOMEN IN ENDOCRINOLOGY: ADDRESSING THE CHALLENGES

WRITTEN BY ANNA CROWN



Who do you see, when you look towards the front of the conference hall, or around the interview panel, or at a management board meeting? Is it the usual group of middle-aged men?

For years there have been equal numbers of men and women entering medicine, and more recently female medical students have been in the majority. However, the higher echelons remain predominantly male. Gender disparities in salaries and clinical excellence awards persist. Such male dominance means that some of the brightest and best entrants to the profession do not achieve their potential, and skews high level decision-making in medicine and clinical research.



Like many of my contemporaries, I was brought up to expect that female gender was irrelevant to my career aspirations. It was during a slightly boozy 'firm night out' during my first senior house officer post that my certainty wavered. The (non-endocrine) professor asked me what my career aims were. When I said I wanted to do academic medicine and have a family, he literally laughed in my face.

I have since been asked at assessments and interviews what I would do if my children had chicken

pox, what I see as the female equivalent of a round of golf, and a range of other mindless and misogynistic questions. I have usually been so taken aback at the time that it has been only afterwards that I have come up with an appropriate riposte. There are still some dinosaurs out there. These are my personal reflections on some of the challenges

'Medicine cannot afford not to benefit fully from the potential of more than half of its recruits'

FAMILY PLANNING

There is never a 'right time' for babies. If you want a career in medicine and a family, you have to manage them 'in parallel', not 'in series'. You cannot take 10 years out to raise a family, then resume a high flying career. If you postpone having children until you have achieved your career aspirations, you risk encountering the heart-breaking world of subfertility.

Many women do experience a subtle attenuation of their personal ambition once they have had children. Previous assumptions about the optimal work-life balance may change. Medics are fortunate to have the option of less than full time (LTFT) training, either job sharing or in a supernumerary post. This is not 'flexible' training: you are working part time but, when rostered to work, you have to be there. It is important to respect your employers and your team. It takes time to organise an LTFT training post, requiring goodwill and planning on both sides, and is not something that can be put in place overnight.

OUT OF HOURS

Unfortunately a lot of important decision-making and succession planning does not happen in meetings or by committee, but after work

in pubs, or at lunchtime on the squash court. This often effectively excludes women with children, for whom the '5-7 pm' time slot is vital to family life. At least if meetings are scheduled 'after work', there will be invitations and minutes, though attendance is still more challenging for those with any domestic responsibilities.

To avoid work flowing over boundaries, women with children may feel they need to limit attendance at national or international meetings and conferences. They may miss out on opportunities for professional development, for making presentations and becoming 'known', and for informal networking.

Some will arrive at a conference having spent the previous weekend food shopping, 'cooking and freezing', and making long lists of reminders about all the domestic issues stored in their mid-brain. Faced with the prospect of a peaceful evening in a hotel room, an uninterrupted bath, and a free choice of TV, the last thing they want to do is go out and socialise.

MUNDANITY AND MULTITASKING

Based on the notion that 'if you want something done, ask a busy woman', many middle-grade women within departments get stuck with repetitive organisational and administrative tasks, further limiting the time and energy they have left for higher level activities.

In competing for promotions or awards, men will often have more confidence (or arrogance), applying even when their qualifications do not quite meet the job description, and 'bigging up' their achievements. Women are more likely to fall victim to the 'imposter syndrome', secretly worrying that sometime soon they will be found out for not being 'up to the job' in some way, attributing success to their team, rather than taking the credit themselves.

TACKLING THE PROBLEM

Both men and women at senior levels in medicine share the responsibility to acknowledge and actively tackle these issues, both implicit and explicit, or the gender disparity will persist. This needs to be intentional and planned; things won't change by chance and our daughters risk finding themselves in exactly the same situation. Medicine cannot afford not to benefit fully from the potential of more than half of its recruits!

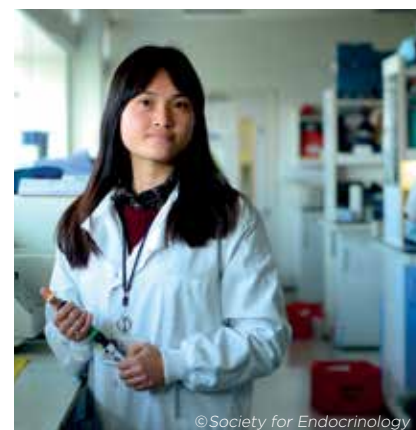
ANNA CROWN

Consultant Endocrinologist and Honorary Clinical Senior Lecturer,
Brighton and Sussex University Hospitals NHS Trust

TELL US YOUR VIEWS

What are your views on the current situation for women in endocrinology?

Send us your thoughts to
[endocrinologist@
endocrinology.org](mailto:endocrinologist@endocrinology.org).



AN INTERVIEW WITH... STEPHEN SHALET

INTERVIEW BY MILES LEVY

I have arranged to meet Stephen Shalet in his flat, which is in a beautiful old converted mill house in the dramatic hills of Derbyshire. His has been a much-touted name for this series of interviews. His pioneering work on the endocrine late effects of childhood cancer treatment is now a major branch of our specialty. He is the key proponent of the concept that there should be a seamless transition between childhood and adult medicine.

Stephen, wearing a patterned jumper and slippers, ushers me up the stairs and plies me with tea and cakes. I am introduced to his second wife, Barbara. I am aware that his first wife died several years ago with myotonic dystrophy – he speaks freely about this during our interview. Stephen has an interesting mix of an imposing physical presence, together with a gentle and attentive manner. He has not lost the north east London lilt from his childhood roots; he is still a die-hard Tottenham fan (shame). The cat jumps onto the table and stares at me with great suspicion as we get going on his master's life story.

EARLY LIFE IN LONDON

Stephen is 70 years old. He looks good on it and still cycles and walks despite a lifetime of sport (he mentions his hip replacement at some point). He was born in Bedford in 1944, but spent his childhood and young adult life in London. His father's side of the family was Ukrainian and his mother's Russian. He lived in the East End and then moved to Stoke Newington, now a fashionable part of London but then mainly populated by Jewish immigrants. He was state-educated at Westminster City Grammar School.

One of four children, Stephen's main influence was his father Montague, a single-handed GP who was 'time poor', juggling work with home: 'Mum's health was indifferent'. He spent his spare time playing with a round ball, as he reflects, 'I was sports mad. I used to play a lot of football and cricket between the houses.'

'Despite this placid dulcet-toned exterior, underneath is a very determined and resilient man'

He decided on medicine at the age of 16. 'My father didn't tell me to be a doctor. He seemed happy and I thought it would make him happy if I was a doctor too. The miracle was that I loved it.' A consistent theme in our interview is how effortless and joyful Stephen found his medical career compared with the uncertainties of life.

Stephen got a place at The London Hospital Medical School, Whitechapel, like his father. Whilst a student, he would go with his dad to Sunday morning GP teaching sessions at the London Jewish Hospital in Stepney Green. 'It was the most wonderful way to learn from famous professors like Harold Ellis', he remarks. Stephen qualified in 1969 and did a surgical

house job at The London: 'I had a belated love affair with surgery.' He soon changed his mind, thinking his technical skills would not be up to scratch. As he puts it, 'I recovered my senses – I'd be up all night worrying about my knots.'

Having done various Senior House Officer jobs, including working for Arnold Bloom (father of famous endocrinologist

son Stephen), he decided on endocrinology. 'As a junior doctor, you are really learning about yourself, how you respond to the disciplines.' Stephen liked the logic of feedback systems; endocrinology was definitely for him and he wasn't shy of telling anyone who would listen.

His Damascene moment came whilst on a teaching course in London. This seems to have been a genuine turning point. 'It all changed for me. I realised I didn't know anything. I wanted to do endocrinology but couldn't have been more ignorant. I decided to do it properly or shut up and do something else.' This betrays a significant personality trait: Stephen does things to perfection or not at all. Despite this placid dulcet-toned exterior, underneath is a very determined and resilient man.

THE MANCHESTER YEARS

To reach his own uncompromising standards, Stephen decided he needed to do proper research. A clinical fellow post became available in Manchester. Colin Beardwell, a respected NHS clinical endocrinologist, would eventually become an important mentor. 'He only appointed me because the two other candidates were mad ... he wanted to know why kids treated for brain tumours appeared to be short.' This research question and the move to Manchester defined a seminal point in Stephen's career and life.

Being a relative imposter as an endocrinologist in a cancer hospital was liberating. He could stay under the radar without anyone bothering him: 'I was walking into a goldmine.' His first paper in *The Lancet* in 1975 described pituitary dysfunction in children with intracranial tumours.¹ He has since published more than 450 papers, hopefully now dispelling his early feelings of inadequacy.

Stephen carefully studied growth hormone (GH) dynamics in cancer-treated children. He describes the now defunct 'Bovril test', saying, 'It probably stimulated GH because it tasted so obnoxious.' He did regular adult endocrinology clinics, and became comfortable treating children despite no formal paediatric training. Stephen reflects, 'It would probably never be allowed in this day and age.' In 1976, he became the first person in the world to treat a child with radiation-induced GH deficiency. Although now commonplace, no one knew at the time whether this was safe. 'As a research fellow I was fearless – it was probably only my ignorance that allowed me to do it.'

Stephen accepts that the advance of late effects endocrinology is due to the triumph of modern oncology. It is only because children were surviving cancer that long term endocrine dysfunction could be studied. 'Initially it was all about GH – but, guess what, children treated for



Stephen Shalet.

cancer also got gonadal failure and thyroid dysfunction, because the neck and gonads got caught in the spinal radiation field.' These were entirely fresh observations, opening a Pandora's box for future publications and research.

CLIMBING THE LADDER

It was now time to get a Senior Registrar post. David Milner, a senior paediatric endocrinologist, advised Shalet to stay in Manchester – he was carving a good reputation from his research. Stephen took his advice and was awarded a senior research grant. In 1978 he was appointed consultant endocrinologist at the Christie Hospital. 'It was a dream job that involved both adult and paediatric endocrinology clinics; I answered to nobody.'

“As a research fellow I was fearless – it was probably only my ignorance that allowed me to do it”

Stephen developed a large adult endocrine practice, the Christie Hospital Endocrine Service becoming a centre of excellence for acromegaly, Cushing's, thyroid cancer and radioiodine clinics. One controversial article from the group was the important original paper suggesting there should be only one regional pituitary surgeon.² 'We had nine surgeons who did pituitary surgery in Manchester at the time and, unsurprisingly, published the worst results in the world!'

Having a background in both adult and paediatric practice was essential in seeing the bigger picture from both sides. Children were commonly being lost to follow up. In highly regarded institutions around the world, children were not receiving GH replacement despite being deficient. The oncologists were unaware of this need, and it became Stephen's mission statement to correct this.



Chemical structure of human growth hormone. ©Shutterstock

WIDER INFLUENCE

Shalet's infectious enthusiasm and passion for this subject have attracted a large number of talented trainees over the years, who are well known to my generation: Andy Toogood, Liz Crowne, Domhnall O'Halloran, Annice Mukkerjee, Rob Murray, Simon Howell, Helena Gleeson, Kate Lissett, Asad Rahim, Peter Clayton, Mandy Ogilvy-Stuart, Mo Didi, Hamish Wallace, Steve Peacey and Ken Darzy. Stephen has clearly had a huge professional and personal influence on them – akin to footballers who have played under the wing of a high profile manager (it is easy to imagine Stephen in sheepskin coat!).

I think Stephen viewed his trainees as both friends and extended family. Mentoring and forging close personal collaborations seems very important to him. His maxim was, 'If you do well, we'll both do well – other than looking after your own money, I'll give you advice whenever you need it.'

The significant areas in which his group has published widely include: the importance of 24-hour GH profiling,^{3,4,5} the re-testing of children transitioning to adult clinics,^{6,7} the number of pituitary deficiencies predicting the likelihood of GH deficiency,⁸ the use of the arginine-GH-releasing hormone test in post-pituitary radiotherapy patients,⁹ and GH neurosecretory dysfunction.¹⁰ These are all accepted areas of endocrine practice, many of which were entirely new at the time.

We then embark on an expansive discussion about the art and science of clinical medicine. I love these parts of the interviews, as it is where I learn so much about the interviewee's subject: better than any 'Meet the Professor' session. Stephen talks about how visceral fat affects GH status. Overweight tired people have low GH dynamics as a result of their weight. He discusses the spectrum of GH deficiency from severe to normality. Despite the rigid numbers used for definitions, cut-off points are arbitrary and there is undoubted overlap between GH-deficient and normal children/adults. I begin to understand more deeply about abnormalities of GH secretion and feel more confident to deal with this area in clinic.

‘He recognised the importance of an endocrine organisation that consisted of both basic scientists and clinical endocrinologists’

A highly collaborative person, Stephen has enjoyed great friendships within endocrinology. He talks particularly highly of John Monson, whom he gives great credit for getting GH accepted by NICE. Monson apparently 'spoke beautifully', whilst defending its merits. He managed to overturn the initial rejection of GH by NICE, based on lack of end-point data.

Stephen describes how the currently accepted quality of life assessment score for adult GH deficiency (the AGHDA) was created. A clinical psychologist at Manchester created the score, which was 'disease-generated rather than disease-specific'. It still baffles Shalet that only one-third of patients with severe GH deficiency have a marked reduction in quality of life, and that there is no linear relationship with the severity of GH deficiency – those with the lowest GH levels do not necessarily feel the worst – 'There must be other factors involved.'

CONTINUED ON PAGE 30...

Stephen has also been very active for the Society for Endocrinology. He was President of the Endocrine Section of the Royal Society of Medicine (RSM), essentially a society for clinicians, and recognised the importance of an endocrine organisation that consisted of both basic scientists in the field of endocrinology and clinical endocrinologists. This did not go down well with an eminent endocrinologist who told him so, whilst standing beside Stephen in the toilet of the RSM. 'You are too nice and are making a big mistake!' Stephen was unfazed, in his own words, 'I ignored him – I refused to be intimidated by a man that admitted to supporting Brighton and Hove Albion!'

FAMILY FORTITUDE

Stephen was made Honorary Professor of The University of Manchester at the age of 50, a very proud day, although 'it didn't change the job in the slightest'. In the background was a constant personal concern. Stephen's wife Caroline had complained of stiffness of her hands in the cold weather when she was in her 30s; this retrospectively had major significance. It was only when their son Daniel was born that the penny dropped. Daniel had delayed developmental milestones, and was diagnosed with myotonic dystrophy at the age of 4. Muscular dystrophy causes difficulty in muscle relaxation, with endocrine (ironically) and heart problems. It is a condition that gets worse down the generations (genetic anticipation) and this explained the timing of onset of the symptoms in his own family members.

"I am shameless in admitting I took strength through their adversities. I saw them as heroes who had to go through much tougher things than me"

Tragically his wife, whom he had met as a teenager in Stamford Hill Jewish Youth Club in London, deteriorated over the years and died at the age of 57 in 2002. He describes his daughter Rachael (whom I know as Shashana) as a miracle. She was born before the family condition was known about, and does not have the gene (there is a 50% chance). Shashana is alive and kicking as a successful senior endocrine nurse at Hope Hospital, Salford, thereby continuing the Shalets' endocrine axis. Daniel has a lot of health problems but manages to work as a machine operator in Cheshire. I sense this is still a great responsibility for Stephen and it reminds me how all families have their own crosses to bear.

Stephen was 59 when his wife died, and this tragedy made him re-evaluate his whole situation. It was now time to consider another way of life. Shalet repeatedly shows an inner resilience and decisiveness at key moments: surely a major reason for his success. He decided that the 'life-cycle' of a research fellow was 5 years and that he would not take on any more, but see out his current trainees properly, before retiring at the age of 62.

CURRENT LIFE

Stephen now has a new life in the middle of the Derbyshire countryside. He has re-married and spends his time cycling, walking, going to the theatre and listening to music; he has a particular passion for Mozart. He has not completely lost his cosmopolitan side. He is keen to point out that the train station is nearby and goes straight to Manchester and Sheffield.

He seems to be at peace with his current situation, but clinical medicine gave him something irreplaceable. 'I miss the stories. I am shameless in admitting I took strength through their adversities. I saw them as heroes who had to go through much tougher things than me.' Stephen still does some medico-legal work and co-chairs a short stature forum (an online educational resource) with Martin Savage, but he has stopped seeing patients.

I have been with Stephen for 4 hours and he kindly offers to take me out for a bite to eat. Before we leave the house, he gives me a book that contains all the 'Hotspur' stories he wrote for *The Endocrinologist* between 2003 and 2012. 'Hotspur' is the pseudonym Stephen used to write anecdotes of clinical and colleague encounters. I have read them since the interview and they are amusing and moving in equal measure. The fact that he chose to write them despite leading a busy life suggests that they must have been a form of catharsis. I would highly recommend going back to the archives if you have not read them.¹¹

As I drive back to Leicester after our gastro-pub bangers and mash, I reflect on Stephen's career and achievements. He has had a major influence on our specialty, more or less starting a whole new clinical branch of endocrinology. Stephen is essentially a social animal and I think about the quiet mill house in the middle of the countryside, and the contrast with the hustle and bustle of his career in central Manchester. Stephen seems happy, and at peace with his new life 'in the third age' as he calls it, but I sense that nothing can quite replace the buzz of medicine. His other passion would have been investigative journalism and I think he would have been good at that.

In his initial email to me when he agreed to take part in our interview, he wrote a telling line which I will leave you with. 'Most people live for the weekend, but I loved Monday mornings. Indeed the passion is such that I have always felt that my work has been a doddle, but life itself is brutally hard.'

MILES LEVY
Editor, *The Endocrinologist*

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2015 VISIONS OF ENDOCRINOLOGY: COMPETITION WINNERS

These are the winners of this year's Visions of Endocrinology competition which encapsulate the breadth and diversity of endocrinology. All winners received a £100 Amazon voucher.

THE BAROMETER OF MY HEART

MARK STOROR,
LEIGHTON SEAL
AND STEPHEN
KING

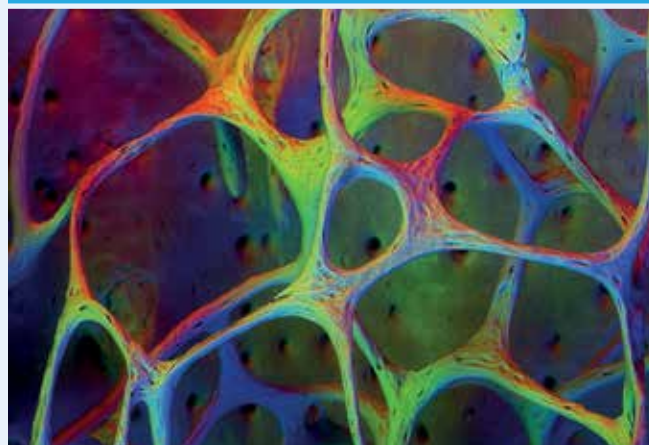
This image is an artistic response to conversations with men attending erectile dysfunction clinics, developed through a collaboration between artist Mark Storor and endocrinologist Leighton Seal.



BACK-SCATTERED SCANNING-ELECTRON MICROSCOPE IMAGE OF BONE

DUNCAN BASSETT, ALAN BOYDE AND
GRAHAM WILLIAMS

The delicate structure of trabecular bone is illustrated in this image by Duncan Bassett, Alan Boyde and Graham Williams. Darker dots are the canaliculi through which osteocytes communicate to sense load, while the roughened surfaces are areas of osteoclastic resorption.



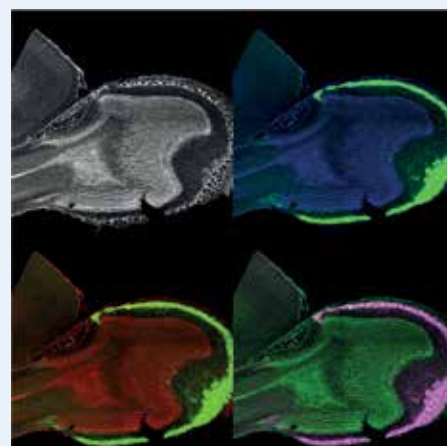
BIOMEDICAL SCIENCES AND ENDOCRINOLOGY

ELINA AKALESTOU

Elina Akalestou's picture is a colourful installation of ELISA plates, which her laboratory uses to detect fluctuations in hormones. Her image reflects the human body, with each major endocrine gland highlighted in a different colour



2015



SAGITTAL SECTION OF A RAT OLFACTORY BULB

RAFAEL PINEDA REYES

Rafael Pineda Reyes' image of a rat olfactory bulb section stained for the enzyme tyrosine hydroxylase is a beautiful approach to show the morphology of neuroanatomical structures involved in endocrine and behavioural regulation.



IN OUR HANDS

STEPHANIE HING

Endocrinology has huge potential to assist conservation efforts, as stress can influence the health and survival of animals, such as this critically endangered Australian marsupial, the woylie, pictured being held by winner Stephanie Hing.

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

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

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

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

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