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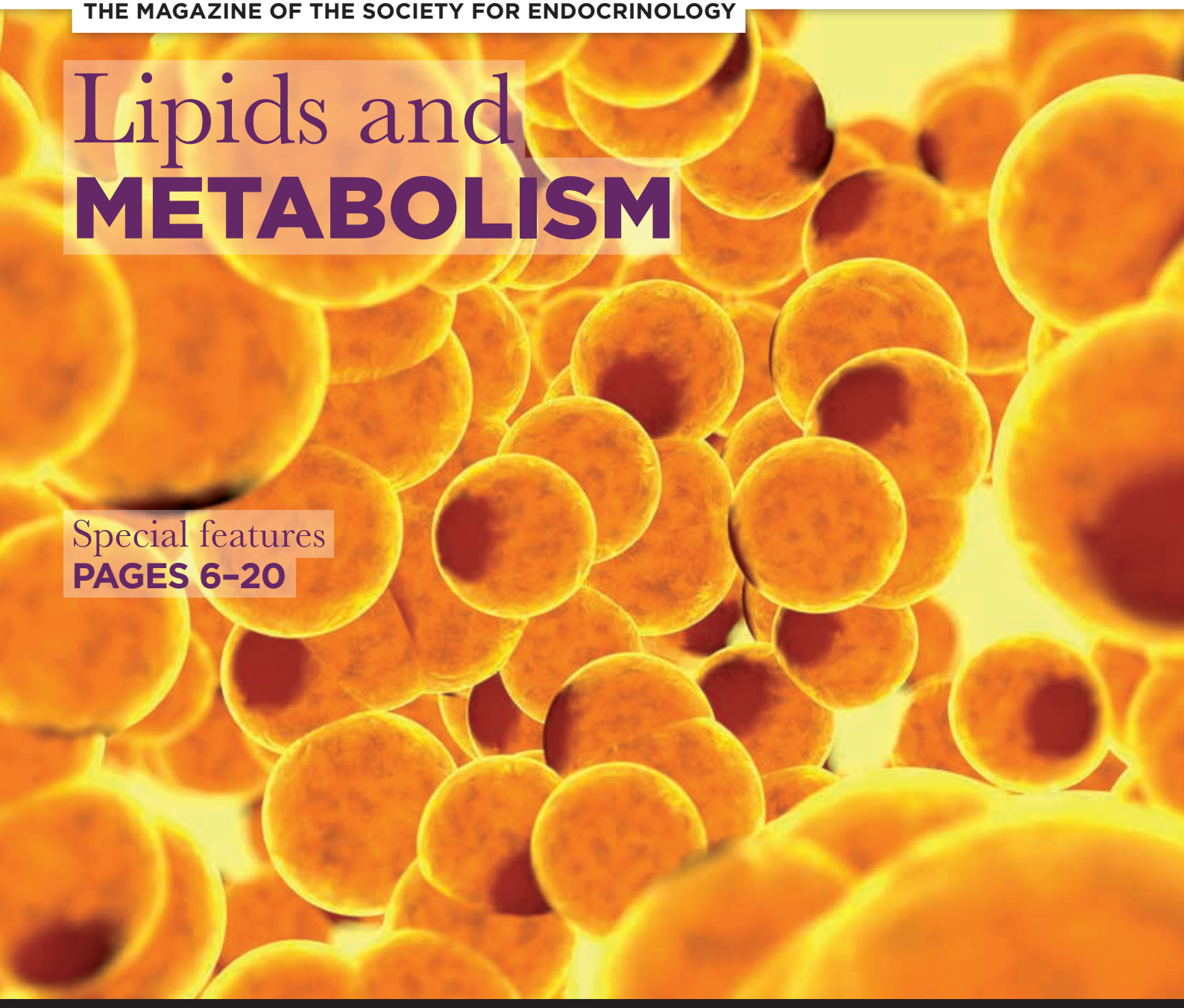
THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY



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A word from THE EDITOR...

A warm welcome to Winter issue of *The Endocrinologist*, which covers the broad and important area of lipids and metabolism, including how they influence and intersect with endocrinological processes and how perturbation can lead to disease.

We have two articles on the controversial topic of 'browning' of white adipose tissue as a potential therapeutic target for obesity (pages 8–11), with differing opinions on its utility. Scientific discoveries require testing and debate. Reading these articles soon after this year's Society for Endocrinology BES conference, I was reminded of the vitamin D debate between Martin Hewison and Naveed Sattar. This provided balanced arguments around the pros and cons of vitamin D supplementation for the population. To advance our understanding, it's important to continue these debates as new data emerge, and to demand evidence and think critically in a measured and analytic way.

Outreach is also an increasingly important activity for us to engage in, and it was inspiring to see the cohorts of schoolchildren interacting with clinicians, nurses and scientists at SfE BES 2022 as they took part in the outreach activities. On pages 28–29, Abigail Byford gives an insightful account of her public engagement journey, which has been enabled by being awarded a Society Public Engagement Grant, and the placenta-printing activities that she co-ordinated at the conference.

With SfE BES 2022 still fresh in our minds, it's hard to not be inspired by Philipp Scherer, recipient of the 2022 Transatlantic Medal. You can read our interview with him on page 14. His career has been a tour de force of adipocyte physiology, with the discovery of the adipocyte secretory factor adiponectin: a major milestone. Whilst not everyone will discover a new hormone in their scientific career, he rightly identifies that there are still plenty of problems to solve along the way!

I wish you a peaceful break over the holiday period.

KIM JONAS

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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 SPRING 2023 issue: **11 January 2023**.

Front cover image ©Shutterstock

Happy holidays to all our readers


Raj Thakker


Márta Korbonits

WITH THANKS

Raj Thakker completed his term as Society President in November. We send him our grateful thanks for all his hard work and dedication during his tenure. We extend a huge welcome to Márta Korbonits, our new President. The 2022 election results were also announced at the AGM. Turn to page 22 to discover who your new Council members and Committee Chairs are.

WATCH AND SHARE OUR PITUITARY GLAND VIDEO

Our fun, educational, animated video on the pituitary gland is available on our public information site, You and Your Hormones, where you will also find a collection of resources that provide useful and accessible facts for schoolchildren and the general public.

The Society's Public Engagement Committee oversee the production of our videos, as part of our key aim of engaging the public with the importance of endocrinology and its impact on their health. Spread the knowledge by sharing the video with your family, friends, school contacts, students and colleagues. Watch it and other videos at **www.yourhormones.info/videos**.

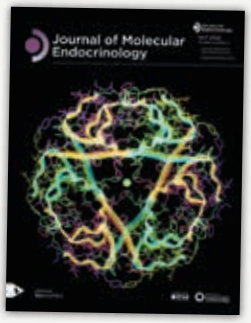
EQUALITY, DIVERSITY AND INCLUSION

The Society's new Equality, diversity and inclusion working group has established two important workstreams:

- to review membership pricing and processes to determine if these may be barriers to joining the Society
- to increase participation of under-represented groups in Society activities.

The group is now preparing a set of recommendations on these areas for review by the wider membership in early 2023. Learn more about the working group at **www.endocrinology.org/edi**.

35 YEARS OF THE RETINOIC ACID RECEPTOR



Don't miss the *Journal of Molecular Endocrinology* special issue, guest-edited by Simak Ali and Vincent Giguère, to celebrate the 35th anniversary of the discovery of the retinoic acid receptor. Read it at **https://jme.bioscientifica.com**.

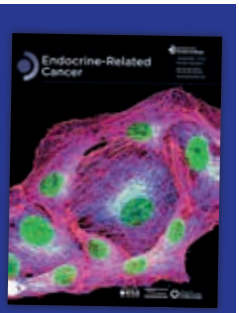
ANOTHER AWARD FOR SOCIETY PODCAST!

Our podcast series, Hormones: The Inside Story, has been 'Highly Commended' in the 2022 Memcom Excellence Awards. The podcast is a hugely successful project, which has made a significant contribution to the Society's aim of informing the public about the role of hormones in all aspects of life. It has also built awareness of our public-friendly website, You and Your Hormones.

Listen, subscribe and share by searching for 'Hormones: The Inside Story' on Apple Podcasts, Google Podcasts, Spotify or wherever you like to listen, or play directly from **www.yourhormones.info/podcast**.

SUBMIT YOUR PAPERS ON GROWTH HORMONE AND CANCER

You have until 1 January 2023 to submit your articles to be included in *Endocrine-Related Cancer*'s special collection focused on 'Growth Hormone in Endocrine Cancers'. Learn more at **https://erc.bioscientifica.com**.



HELP IMPROVE SCIENCE REPORTING IN THE MEDIA

Become a Society Media Ambassador to share your expertise with journalists and help them to report more responsibly and accurately on endocrinology-related topics in the news. Find out more at **www.endocrinology.org/engaging-with-the-media**.

SOCIETY CALENDAR

24 March 2023
NATIONAL CLINICAL CASES
London, UK

ENDOCRINE ACADEMY

24 April 2023
Clinical Update

25 April 2023
Endocrine Nurse Update
Birmingham, UK

13–15 November 2023
SfE BES 2023
Glasgow, UK

www.endocrinology.org/events for full details

GRANT AND PRIZE DEADLINES

8 March 2023
SUMMER STUDENTSHIP GRANT

8 March 2023
TRAVEL GRANT

22 March 2023
PUBLIC ENGAGEMENT GRANT

31 March 2023
ESA-SfE EXCHANGE AWARD

5 April 2023
PRACTICAL SKILLS GRANT

12 April 2023
LEADERSHIP & DEVELOPMENT AWARDS PROGRAMME

26 April 2023
STUDENT VIDEO AWARD

26 April 2023
UNDERGRADUATE ACHIEVEMENT AWARD

3 May 2023
EARLY CAREER GRANT

3 May 2023
EQUIPMENT GRANT

17 May 2023
ENDOCRINE NURSE GRANT

17 May 2023
MEETING SUPPORT GRANT

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

HOT TOPICS

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via the Members' Area on the Society website, **www.endocrinology.org**. *Endocrine Connections*, *Endocrinology, Diabetes & Metabolism Case Reports* and *Endocrine Oncology* are open access and free to all. Publishing in *Endocrine Oncology* is currently free.

JOURNAL OF ENDOCRINOLOGY

11β-HSD1 and age-related metabolic decline

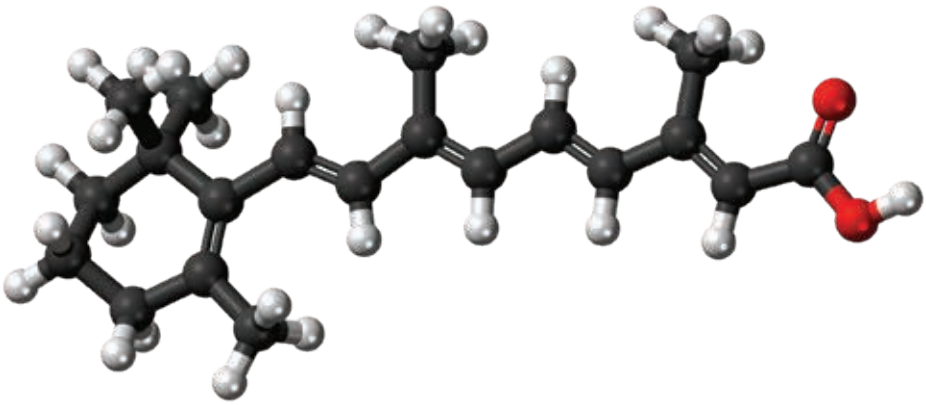
Ageing sees a widespread decline in biological function. This is driven by a range of molecular dysregulation leading to progressive failure of body organs and homeostatic systems. Though our understanding of these processes is partial, insights into ageing are advancing.

The glucocorticoid class of steroid hormones is fundamental for life and central to human health. Age-related increase in the pre-receptor generation of intracellular glucocorticoids, by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), has been observed in a variety of cell and tissue types. However, its impact within the context of whole body functioning and vital physiological parameters remained untested.

Here, Morgan *et al.* used genetic ablation of *11BHSD1* in mice of young and aged cohorts to elevate our understanding of how glucocorticoids, and a lifetime's exposure to them, impact tissue weight, tissue function and overall health. Using these data, they demonstrated that selective 11β-HSD1 inhibition may yet prove fruitful as a strategy in the search for the preservation of the human health-span.

Read the full article in *Journal of Endocrinology* **255** 117–129

JOURNAL OF MOLECULAR ENDOCRINOLOGY



Retinoic acid. Jynto/CC0

Chronicle of a discovery: the retinoic acid receptor

This review by Giguère and Evans appears in a special issue of *Journal of Molecular Endocrinology*, which has collected articles to reflect on the retinoic acid receptor, in celebration of 35 years since its discovery. The discovery initially came about as a surprise, but brought together whole streams of medical science and understanding, ultimately helping us understand the methods of action of vitamin A.

Through this review, we revisit the history and background of the identification of the receptor and are taken nicely through the timeline of its impact. Bringing the tale right up to the modern day, we see how studies of the retinoic acid receptor are still covering new ground in terms of understanding disease and disease therapeutics. It is a fantastic summary, which leads nicely into the rest of the special issue.

Read the full article in *Journal of Molecular Endocrinology* **69** T1–T11

ENDOCRINE-RELATED CANCER

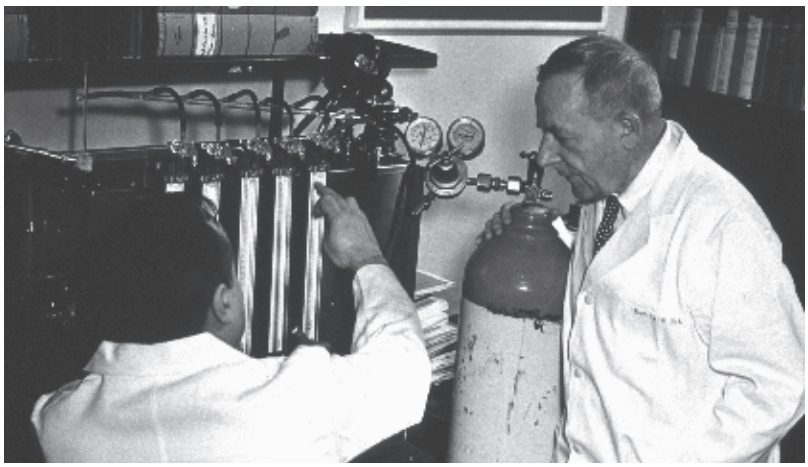
100 years of the Warburg effect

To coincide with the centenary of Otto Warburg's description of tumour cells producing lactate even in the presence of oxygen, *Endocrine-Related Cancer* has focused on collecting papers dedicated to this finding and its overall impact.

All contributions here are worth reading, but we have decided to highlight the introductory article by Hardie. He takes us through the early life of Otto Warburg, including his early education, and learn how war ultimately hampered his progress. Fortunately, he returned to science, and this piece nicely showcases his studies on the metabolism of cancer cells through fermentation and respiration. It also highlights the range of techniques available at the time.

The article goes to show the lengths to which Warburg went to undertake a fundamental experiment which has shaped a lot of our physiological understanding to date. It shows a side of this work that I hadn't truly appreciated before, and it should be required reading for anyone involved in the field of medicine.

Read the full article in *Endocrine-Related Cancer* **29** T1–T13



Otto Warburg (right) with assistant. Public domain image from the National Library of Medicine digital collection, http://resource.nlm.nih.gov/101442335

Hot Topics is written by Sophie Clarke, Craig Doig, Louise Hunter, Gareth Nye and Venkatram Subramanian.

HT

CLINICAL ENDOCRINOLOGY

A practical guide to genetic testing in endocrinology

This article outlines a practical means of understanding different types of genetic testing for use in the consulting room. Izatt and colleagues have used an example case study to represent the approach for a 'standard patient'. They then proceed to explain various testing methods and give a brief description of the role of genetic testing in the management of a range of hereditary endocrinological conditions.

Consideration is also given to talking about the results with patients and their families, including difficulties in discussions regarding pregnancy planning and understanding the likelihood of transmissibility between generations.

The figures are quite useful in summarising the information outlined in the article. This guide should support clinicians who are trying to gain an understanding and incorporate this into their clinical practice, where applicable.

Read the full article in *Clinical Endocrinology* **97** 388–399

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Handling severe hyperparathyroidism in pregnancy

Managing endocrine conditions during pregnancy can be challenging. Beck and colleagues present the case of a 26-year-old woman who presented at clinic with hypercalcaemia. Subsequent investigations supported a diagnosis of primary hyperparathyroidism due to a right-sided parathyroid adenoma. Her planned surgery was delayed due to the COVID-19 pandemic.

Subsequently, the patient presented with hyperemesis and dehydration when eight weeks pregnant, with a serum calcium of 3.48mmol/l. This hypercalcaemia did not improve substantially with rehydration. Severe hypercalcaemia in pregnancy presents risks to both maternal and fetal health. However, historically, parathyroidectomy is offered in the second trimester, because of the perceived risks of anaesthesia earlier in pregnancy.

In this case, after weighing benefits and risks, it was decided to proceed with parathyroidectomy in the first trimester, under local anaesthetic.

This procedure proceeded successfully, with immediate resolution of hypercalcaemia and symptoms post-operatively. The patient remained normocalcaemic for the remainder of the pregnancy, and her baby was found to have a normal calcium level at delivery.

In their useful discussion, the authors highlight different options for managing primary hyperparathyroidism in pregnancy, and discuss the evidence base regarding timing of intervention.

Read the full article at *Endocrinology, Diabetes & Metabolism Case Reports* doi: 10.1530/EDM-21-0203

ENDOCRINE CONNECTIONS

Immunoassay may not reveal low aldosterone in COVID-19

Accurate detection and quantification of hormones is critical to proper disease management. Patient hormone levels are determined by the gold standard of liquid chromatography with tandem mass spectrometry (LC/MS-MS) or biochemical detection using immune assays, such as enzyme-linked immunosorbent assays.

During the recent COVID-19 pandemic, low aldosterone/renin ratios have been considered as predictive of increased disease severity. Wiegand *et al.* report how, through use of LC/MS-MS, staff at Cambridge University Hospitals observed reduced aldosterone in a significant cohort of patients with COVID-19. The team applied both LC/MS-MS and immunoassay methods to better describe the disparity between the two methods of aldosterone detection. They reveal an underlying issue with a common clinical immunoassay that may result in false readings for the detection of aldosterone.

Their work demonstrates that there is probably a sizable cohort of patients with COVID-19 for whom reduced aldosterone levels have remained undetected.

Read the full article in *Endocrine Connections* **11** e220190

ENDOCRINE HIGHLIGHTS

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

Explaining hyperandrogenaemia in Cushing's disease

Cushing's disease (CD) is caused by cortisol excess due to excess adrenocorticotrophin (ACTH) secretion, predominantly due to pituitary tumours. It is often associated with symptoms consistent with hyperandrogenism. However, such symptoms are insufficiently explained by serum androgen levels. 11-Oxygenated C19 (11oxC19) steroids are adrenally derived and stimulated by ACTH.

To investigate whether 11oxC19 steroids may explain the clinical hyperandrogenism observed in CD, Nowotny and colleagues undertook salivary day profiles in women with CD before (n=23) and after (n=13) successful transsphenoidal surgery, as well as in five women with CD treated with metyrapone and five treated with osilodrostat. In addition, 24-h urinary analysis was undertaken.

Pretreatment, women with CD had a significantly elevated AUC of salivary 11oxC19 steroids, including increased 11-hydroxyandrostenedione (11OHA4), compared with controls, as well as an increased AUC of salivary 11-ketotestosterone (11KT). Testosterone, androstenedione and dehydroepiandrosterone sulfate levels were comparable with controls. After transsphenoidal surgery, 11OHA4 and 11KT and urinary 11-oxo-androsterone were all significantly reduced, compared with preoperative levels. Both osilodrostat and metyrapone blocked 11oxC19 synthesis.

These data suggest that the active androgens responsible for clinical hyperandrogenism in patients with CD are predominantly ACTH-mediated 11oxC19 steroids.

Read the full article in *European Journal of Endocrinology* **187** 663–673

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MANAGEMENT OF INHERITED DYSLIPIDAEMIA

WRITTEN BY WEI YANG AND JAIMINI CEGLA

Inherited dyslipidaemia can be monogenic or polygenic. There are around 25 well-established monogenic dyslipidaemias. Familial hypercholesterolaemia, the best-known monogenic dyslipidaemia, is an autosomal dominant condition, associated with a raised low-density lipoprotein (LDL) cholesterol level and, consequently, accelerated atherosclerosis. Polygenic dyslipidaemias, on the other hand, result from multiple common genetic variations. Genetic testing is beneficial for the diagnosis of suspected monogenic dyslipidaemias, with cascade testing available for family members of confirmed cases.[1]

TRADITIONAL TREATMENTS FOR INHERITED DYSLIPIDAEMIAS

Statins[2]

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a key enzyme in cholesterol production in the liver, to upregulate the LDL receptor and reduce the LDL cholesterol level in the circulation.

Statin treatment is generally well-tolerated. However, perceived statin intolerance is a major problem. The efficacy and safety of statins for the primary and secondary prevention of cardiovascular diseases are also well-established.

High intensity statin therapy (such as atorvastatin 80mg/day or rosuvastatin 40mg/day) can lower LDL cholesterol by up to 60%. However, alone, this is insufficient to achieve guideline-recommended LDL cholesterol levels in most cases of familial hypercholesterolaemia.

Ezetimibe[3]

Ezetimibe blocks Niemann–Pick C1-like 1 protein, to inhibit intestinal cholesterol absorption. It can decrease LDL cholesterol by around 20%. It is a safe and efficacious agent used either as a monotherapy or as an add-on to a statin.

Fibrates[4]

The main effect of fibrates (peroxisome proliferator-activated receptor-α agonists) is the reduction of triglycerides. They can lower triglyceride levels by reducing production by the liver and by speeding up their removal.

Although fibrates do not show much effect in lowering LDL cholesterol, they can be used in combination with a statin in patients suffering both high LDL cholesterol and high triglycerides. Fenofibrate does not interfere with the metabolism of statins and is considered the safest fibrate to use with a statin, if necessary.

Lipoprotein apheresis[5]

This is a highly efficient, but time-consuming and expensive, method for removal of excessive lipoproteins from the blood, including LDL cholesterol, lipoprotein(a) and triglyceride-rich lipoproteins. For half a century, it has been the therapy of last resort for dyslipidaemias that cannot otherwise be controlled.

Although new potent lipid-lowering drugs have recently been introduced, lipoprotein apheresis still plays an important role in managing homozygous familial hypercholesterolaemia and, less often, other forms of dyslipidaemia.

NOVEL LIPID-LOWERING MEDICATIONS

PCSK9 monoclonal antibodies[6]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) protein helps to breakdown LDL cholesterol receptors, so more cholesterol can remain in the bloodstream. Human PCSK9 monoclonal antibodies, evolocumab and alirocumab, were introduced to the UK market in 2016. They can lower LDL cholesterol levels by up to 75% and significantly reduce cardiovascular risk.

Aggressive lowering of LDL cholesterol by PCSK9 monoclonal antibodies has been accompanied by a favourable safety profile. NICE guidelines recommend that PCSK9 monoclonal antibodies are considered in patients with familial hypercholesterolaemia if LDL cholesterol is >5mmol/l in primary prevention and >3.5mmol/l in secondary prevention. PCSK9 monoclonal antibodies are administered every two weeks as a subcutaneous injection.

Inclisiran[7]

Inclisiran is a novel small interfering RNA which prevents the production of PCSK9 protein. It is the first small interfering RNA-based therapy in the area of cardiovascular disease, and lowers LDL cholesterol by around 50%.

Inclisiran was introduced to the UK last year. It has safety data for up to three years, and the evidence is accumulating for its long term use. However, long term cardiovascular outcome data are still awaited.

NICE guidance has recommended inclisiran for patients with established cardiovascular disease if LDL cholesterol is persistently >2.6mmol/l. Compared with PCSK9 monoclonal antibodies, the dosing regimen of inclisiran (initial, three-month booster and then six-monthly subcutaneous injection) has the advantage of allowing administration by healthcare professionals and consequently increased adherence.

Bempedoic acid[8]

Bempedoic acid inhibits ATP citrate lyase, an enzyme upstream of HMG-CoA reductase, in the cholesterol synthesis pathway. It is a daily-dosing oral tablet that reduces LDL cholesterol by around 25% when given alone, and by around 40% when given in a fixed-dose combination with ezetimibe.

Bempedoic acid is a pro-drug which is converted to the active form mostly in the liver. This limits the muscle-related side effects when compared with statins. NICE guidance has recommended the use of bempedoic acid in patients who cannot tolerate statins or fail to achieve treatment targets with statin treatment.

NEW HORIZONS

In these ways, several new treatment options have recently become available for patients with inherited dyslipidaemias. The future may include therapies based on gene editing to combat these conditions. CRISPR gene editing targeted at PCSK9 may represent a promising tool to achieve lifelong LDL cholesterol reduction.[9,10]

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HYPOTHALAMIC LINKS BETWEEN GROWTH AND ENERGY BALANCE

WRITTEN BY REBECCA DUMBELL

Growth is an intrinsic part of energy balance. To fuel growth, there must be enough consumption of food. This is evident to anyone who has been around growing teenagers. However, there is evidence in humans and model species that these links persist across the lifespan and have consequences for metabolic health and disease.[1]

Understanding of the hypothalamic–pituitary–growth axis began over 100 years ago, with experiments isolating growth hormone (GH) from the pituitary glands of cows, and early investigations into spontaneous mouse mutants date back as far back as the 1920s. The release of GH from the pituitary is regulated in the hypothalamus by means of pulsatile secretion of inhibitory somatostatin from neurones of the periventricular nucleus, and production of the stimulatory GH-releasing hormone from neurones of the arcuate nucleus, reaching the pituitary through the hypophyseal blood portal system.

THE INVOLVEMENT OF EXERCISE

Stimulation of the growth axis by exercise is something that we explored in the seasonally adapted Siberian hamster (*Phodopus sungorus*), which has long been purported to be a model for reversible obesity. This dwarf hamster species, native to the Kazakh and Mongolian–Manchurian Steppe, undergoes 'Dehnel's phenomenon', where their body size (and consequently energy requirements) reduces in anticipation of winter.

The physiological changes these hamsters go through include cessation of reproductive capacity, voluntary reduction in food intake, and reduction in body weight (both lean and fat mass), bone mineral density and femur length, organ size (testes/ovaries, liver, kidney, skeletal muscle, adipose tissue depots), in addition to the endearing development of a thick white fur, which even covers the soles of their feet.

Although it had been established that the central thyroid hormone axis is key to this suite of seasonal physiological changes, we demonstrated that the hypothalamic–growth axis, particularly the somatostatin neurones of the arcuate nucleus, is probably key to driving these *growth* changes.[2] Similarly, growth can be stimulated in these 'winter-adapted' hamsters with voluntary exercise on a running wheel; they gain lean and fat mass in equal proportion which, again, we attributed to stimulation of the growth axis.[3]

This could be a model for what happens in human physiology in response to an exercise intervention which, without accompanying dietary intervention, is often followed by weight gain rather than the expected loss. Therefore, understanding how exercise may stimulate food intake will help improve exercise-driven weight loss interventions.

LINKS TO NUTRITION

In more recent work, we again found that arcuate nucleus somatostatin may play a role in small body size. There is proportionately lower body fat and food intake in mice with a mutation in the ZFHX3 transcription factor, which appears to model a similar protein-altering mutation in a human population.[4] This suggests that these arcuate nucleus somatostatin neurones, not previously considered important in the regulation of GH secretion, may have a conserved role in long term growth and energy balance.

GH is a 'fasting hormone', released mainly during the night in humans. It helps regulate glucose levels by stimulating lipolysis to increase free fatty acids in circulation and drive lipid metabolism. Selective loss of GH receptor in adipose tissue leads to increased fat mass in mouse genetic models,[5] indicating direct action at the tissue. Results are, however, less clear for insulin-like growth factor-1, probably due to the limitations of selective genetic manipulations.

Hypoglycaemia probably influences the growth axis by stimulating neuropeptide Y (NPY) neurones of the hypothalamus which, while NPY is predominantly known for its appetite-stimulating action, also stimulates upregulation of the positive arm of the growth axis.[6]

Signals from the periphery, such as glucose, other nutrients, vitamins and hormones, reach the brain through 'leaky' regions in the blood brain barrier – the circumventricular organs such as the median eminence, and specialised cells called tanycytes that can relay nutrient signals from the cerebrospinal fluid to the hypothalamus.[7] This makes these specialised cells, which even contain taste receptors,[8] key for relaying nutrient signals to influence energy balance in the brain, and allows for regions close to these 'leaky' sites to be influenced by peripheral nutritional status. The recent discovery of novel blood portal systems[9] means that brain regions that we didn't previously consider may be able to respond to such nutrient signals.

'Understanding how exercise may stimulate food intake will help improve exercise-driven weight loss interventions.'

Interestingly, interactions with macronutrient preference in the diet have been identified in rats who had GH-releasing hormone or somatostatin manipulated in the hypothalamus. A human genome-wide association study identified a variant in the somatostatin SST2 receptor associated with protein content in the diet and body mass index.[10] This link between dietary protein and growth axis activity makes sense on an intuitive level, and suggests that links between the growth axis and eating behaviour may be even more complex than simply responding to glucose status.

Going forward, it is exciting to consider that systems studied for over a century still have more to tell us about how the brain integrates peripheral signals, whether from diet, exercise or the environment, to drive growth, eating behaviour and glucose and lipid metabolism. Understanding these systems will lead to better interventions to regulate body weight and tackle metabolic disease.

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ADIPOSE TISSUE: DIVERSE AND DISTINCT ROLES IN METABOLIC HEALTH

WRITTEN BY KARLA JADE SUCHACKI

Karla Jade Suchacki gave the 2022 Early Career Prize Lecture for basic science at SfE BES 2022 in Harrogate. We are delighted to include this summary of her talk here.

Obesity and its associated co-morbidities, including cardiometabolic complications (e.g. type 2 diabetes mellitus, hypertension and cardiovascular disease), substantially contribute to negative global health outcomes. The key feature of obesity is increased white adipose tissue (WAT) mass; the role of 'lesser known' adipose depots, such as brown adipose tissue (BAT) and bone marrow adipose tissue (BMAT), is not clear in adult humans.

WAT is typically classified into visceral and subcutaneous depots that are dispersed throughout the body. As the primary organ of lipid storage, WAT is characterised by large monolocular lipid droplets, and plays a key role in systemic energy homoeostasis. It also has important endocrine and immunological roles (Figure).[1]

'Inhibition of peripheral serotonin synthesis may be a novel strategy to treat obesity-associated metabolic disease.'

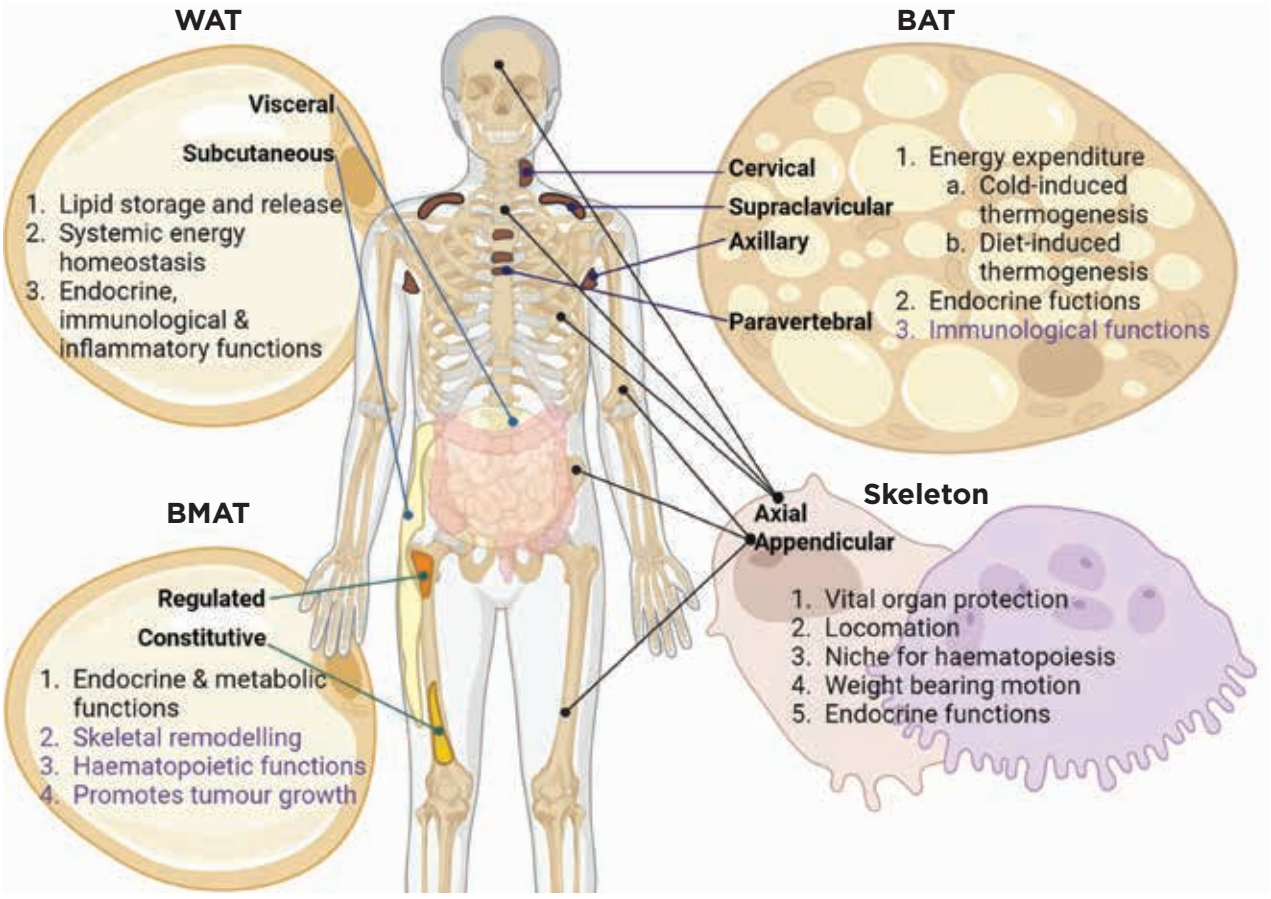
BROWN ADIPOSE TISSUE

In contrast to white adipocytes (WAds), brown adipocytes (BAds) contain multilocular lipid droplets, are rich in mitochondria and express uncoupling protein 1, which generates heat by uncoupling the electron transport chain. Therefore, BAT is a thermogenic organ that increases energy expenditure to maintain body temperature in a cold environment (Figure).

In adult humans, functional BAT was identified about 20 years ago, when positron emission tomography/computed tomography (PET/CT) using the metabolic tracer ^{18}F-fluorodeoxyglucose (^{18}F-FDG) led to its incidental identification.[2] BAT is now known to be located in the neck, supraclavicular, paravertebral, peri-aortic and perirenal regions.

BAT activation improves insulin sensitivity and lipid clearance, highlighting its beneficial role in metabolic health. Furthermore, BAT activity is substantially reduced in obesity and type 2 diabetes mellitus. However, repeated cold exposure increases BAT mass and activity in subjects with obesity or type 2 diabetes mellitus, and can reduce WAT

Figure. The distribution and function of WAT, BAT, BMAT and the skeleton. Each depot has specific roles as indicated, with putative functions highlighted in purple. In the skeleton, the bone-forming osteoblasts (pink) and bone-resorbing osteoclasts (purple) are shown. Created in BioRender



mass.[3] Thus, activating BAT is an exciting approach to treating obesity and metabolic disease.

UNDERSTANDING BAT

Our understanding of human BAT remains in its infancy, and the regulation of human and murine BAT activation is not always preserved between the two species.[4] Using transcriptomics of human BAds, we have recently identified the serotonergic system as a key regulator of human BAT, and inhibition of peripheral serotonin synthesis may be a novel strategy to treat obesity-associated metabolic disease.

Furthermore, accurately quantifying BAT mass in humans is challenging, as estimates of BAT activity are based on substrate consumption, with no specific imaging biomarker for BAT reported. To address this, we have recently identified a novel PET tracer that can identify BAT without cold or drug stimulation in humans. In addition, novel PET tracers have the potential to provide mechanistic insights and improve our understanding of human BAT activation. To date, factors/agents that improve murine BAT function have failed to translate to humans, hence understanding of the regulation of human BAT is key to identifying novel pathways amenable to therapeutic manipulation.

BONE MARROW ADIPOSE TISSUE

BMAT is another unique adipose tissue depot that has been largely ignored since its identification over a century ago. Situated within the marrow cavity, BMAT constitutes approximately 70% of bone marrow volume (and approximately 10% of total adipose tissue mass) in healthy adult humans, principally in the appendicular skeleton.[5]

In contrast to WAds, bone marrow adipocytes (BMAds) proliferate in conditions such as anorexia nervosa and type 1 diabetes. BMAds exist in two subtypes: 'constitutive' BMAds that predominate at distal skeletal sites, and 'regulated' BMAds which are interspersed within the haematopoietic bone marrow at proximal skeletal sites and within the axial skeleton. BMAds are morphologically similar to WAds, having a large unilocular lipid droplet; they produce adipokines (leptin and adiponectin) and release free fatty acids in response to lipolytic stimuli (Figure).

THE ROLE OF BMAT

We recently showed that BMAT plays a key role in glucose clearance and is functionally distinct from WAT and BAT.[6] Using ^{18}F-FDG PET/CT, we revealed that BMAT resists both insulin- and cold-stimulated glucose uptake. Highlighting its key metabolic role, glucose uptake by BMAT is greater than is found in the axial bones or in WAT, and can even exceed skeletal muscle uptake.[6]

> ***'Glucose uptake by bone marrow adipose tissue is greater than is found in the axial bones or in white adipose tissue, and can even exceed skeletal muscle uptake.'***

Finally, BMAT is situated within the bone marrow cavity and, through total body PET, we have recently determined that different bones within the skeleton have a unique glucose metabolism and form a complex metabolic network.[7] In addition to the classical functions of the skeleton, both rodent and human studies have identified the skeleton as a key endocrine regulator of metabolism.[8]

These data highlight the need to broaden our focus beyond individual adipose depots, taking a whole body approach. As we continue to develop new analytical approaches to understand complex tissue interactions at a systems level, this will improve our ability to better understand mechanisms underlying metabolic disease and develop novel therapeutics.

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SWITCHING ON BAT TO TREAT OBESITY: A FLAWED STRATEGY?

WRITTEN BY JOHN R SPEAKMAN

An enormous amount of research effort is currently being directed at understanding the factors that regulate activation of brown adipose tissue (BAT), and the conversion of beige adipocytes from their white to their brown phenotype: the browning of white adipose tissue (WAT).[1] The principal aim of this work is to find drugs or other interventions that can switch on BAT or cause browning of WAT in humans, to stimulate energy expenditure and burn off lipids, thereby reducing the level of obesity. There is, however, some worrying evidence that the whole approach of switching on BAT may be flawed.

An argument supporting the research effort is that cross-sectional studies in humans show that individuals with more BAT have less WAT.[2] However, the direction of causality in that relationship remains unclear. It could be that high levels of BAT do indeed stimulate expenditure and burn off WAT. But an alternative, and equally tenable, hypothesis is that the insulation provided by large amounts of WAT reduces the thermoregulatory requirement to activate BAT.[3]

BAT AND COLD EXPOSURE

BAT is responsive to cold exposure, and there is a seasonal cycle of BAT activation in temperate regions. If activated BAT leads to reduced WAT, then one would predict that there would be an association between the average annual ambient temperature of a location and the prevalence of obesity there. Six years ago, we merged data on the age-normalised prevalence of obesity across the 3000+ counties in the mainland USA and data on the ambient temperature in each county, and found that there is no association between obesity prevalence and temperature.[4]

Surprisingly, however, there was an effect of temperature on the prevalence of type 2 diabetes. This was a big effect, explaining more than 25% of the variation in the prevalence of the condition, more than the variance explained by all the genetic targets for type 2 diabetes combined!

WHY ELEVATED BAT MAY NOT LOWER OBESITY

Does this mean switching on BAT to treat obesity won't work? Possibly, but it's not clear cut. There are several reasons why elevated BAT activity might not translate to lowered obesity rates. The first is that increased energy demands from activated BAT may stimulate food intake. This seems to be a major reason why increasing physical activity energy expenditure (AEE) is not very effective for weight loss. A second problem is that activating BAT might be offset by changes in other components of the energy budget, like AEE. These effects would compromise the utilisation of activation of BAT as a strategy to combat obesity.

Another possibility, however, is that humans have a unique capacity to buffer environmental impacts on expenditure, by modifying their environment and rapidly changing their external insulation (clothing). These are options that are unavailable to most other mammals.

AMBIENT TEMPERATURE AND FREE-LIVING ENERGY EXPENDITURE

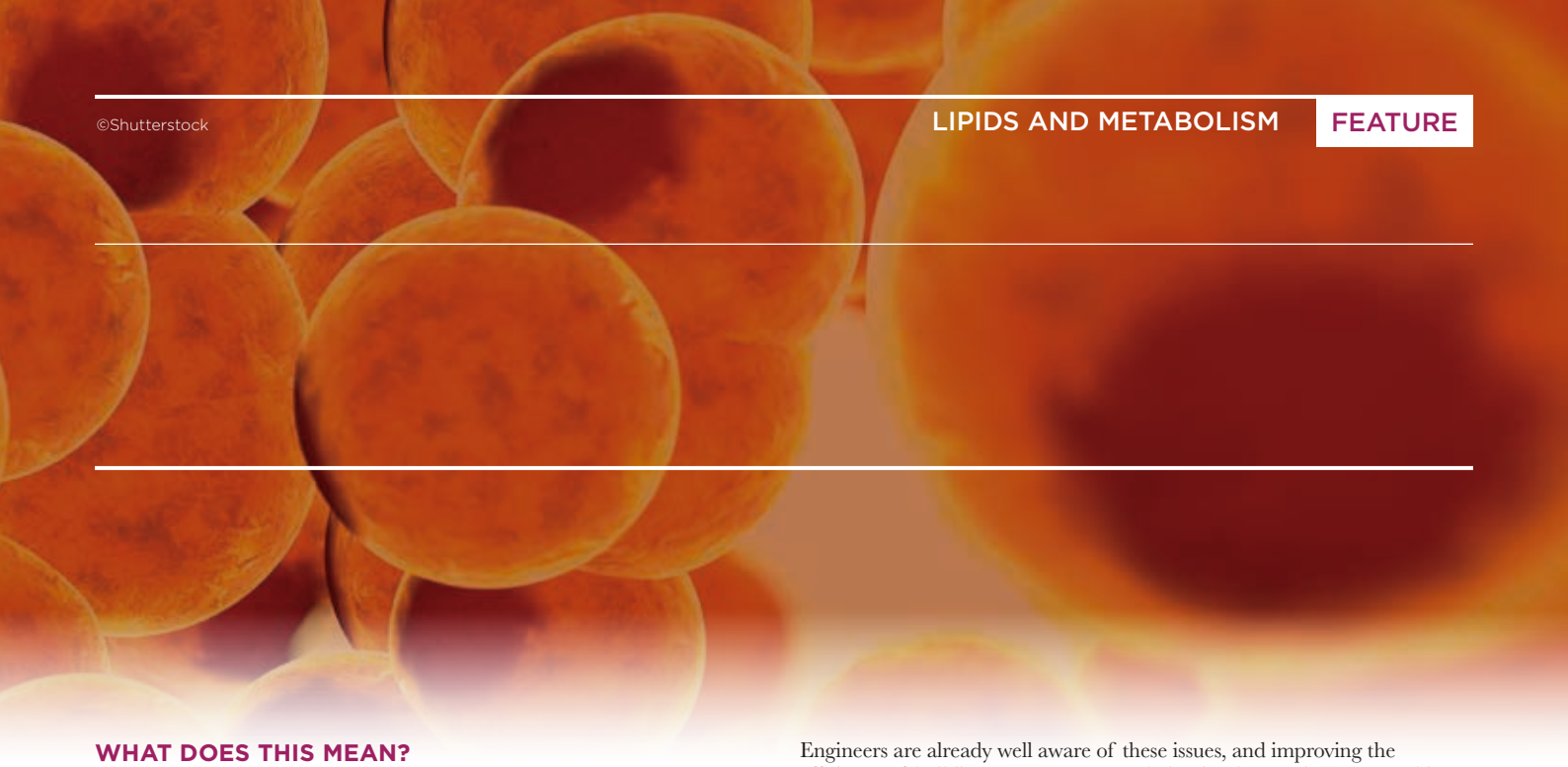
The impact of ambient temperature changes on free-living energy expenditure was, until recently, unknown. This is because the gold standard, doubly labelled water (DLW) method for measuring such changes is expensive, and has generally been applied to small samples. Even when large samples have been measured, these have come from geographically restricted areas.

The pooling of DLW data in a large international database sponsored by the International Atomic Energy Agency[5] has opened up the opportunity to explore the role of ambient temperature effects on total energy expenditure (TEE). Such an analysis based on more than 3000 measures of TEE across the USA has just been published.[6]

These data show that, although the ambient temperature varied between −10°C and +30°C, there was no relationship at all between the TEE and temperature. Moreover, when the data were split down into basal and activity expenditure, there were no trends in these either. This suggests any cold-induced increases in basal expenditure due to activating BAT were not being offset by lowered AEE to keep the total constant. Much more likely was that the expenditure was not being stimulated at all by the cold, due to the buffering effects.

> *'Humans have a unique capacity to buffer environmental impacts, by modifying their environment and rapidly changing their external insulation (clothing).'*

Supporting this idea, a review of the temperatures inside buildings showed that these are sustained over a much narrower range, between 18°C and 25°C, independent of the temperature outside. Humans buffer their exposure to cold by not going outside very much, wearing clothing that mitigates any effects when outside, and keeping the temperatures inside their homes and workspaces at a temperature that does not necessitate large amounts of themoregulatory heat production. Consequently, TEE is independent of ambient temperature, and that is probably the main reason why we didn't previously find any link between ambient temperature and the prevalence of obesity.



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WHAT DOES THIS MEAN?

This work has several implications. The first is that, because there is no relationship between TEE and ambient temperature, the absence of a relationship between ambient temperature and obesity prevalence cannot be used as an argument that switching on BAT will not work as an anti-obesity strategy.

'Impacting two of the biggest current issues on the planet (obesity and climate change) may be as simple as turning down the thermostat dial in your living room!'

Secondly, humans routinely occupied building spaces at temperatures between 18°C and 25°C. That is somewhat lower than the thermoneutral zone for lightly clothed humans of 23°C to 30°C.[7] Humans live at these sub-thermoneutral temperatures, probably because this is the optimal temperature to dissipate their heat production generated from a combination of basal and activity expenditure. In contrast, thermoneutral temperatures are optimal only to dissipate basal expenditure. Because humans do not routinely exist at basal metabolism and live at thermoneutral, then the argument that we should keep mice at 30°C (mouse thermoneutral),[8] and that this will provide maximal translational efficiency to humans, makes no sense. Rather, keeping mice a few degrees below their thermoneutral temperature would seem a much better option to maximise translational relevance of mouse models.[9]

A WIDER PERSPECTIVE

Finally, there are some wider ramifications of this work that extend far beyond the realms of endocrinology and physiology. By engineering their environments, humans are able to stay in a comfortable temperature, despite the temperature outside fluctuating enormously. The measures of TEE show that this is a phenomenally successful strategy. Whether this pattern is also evident in populations that do not have access to air-conditioning and heating is interesting but, at the moment, we do not have a large enough sample of TEE data from such communities to test the idea.

Manipulating our environment to avoid having to thermoregulate comes at a huge energy cost. The energy demands for heating and cooling buildings to keep them in our comfort zone occupies between 18% and 73% of total building energy use.[10] In 2010, the building sector accounted for 32% of global energy demand and 30% of energy-related CO_2 emissions.

Engineers are already well aware of these issues, and improving the efficiency of building temperature regulation is a key goal. However, this debate has largely proceeded on the assumption that we have to keep buildings at their current temperatures and then focus on how to achieve that by adjusting building insulation and efficiency. Comparatively little effort has been directed towards understanding what the consequences might be of shifting the burden of thermoregulation away from buildings and back onto individuals.

This is not a simple calculation. Increasing individual energy demands could require greater food intake, and hence increases in the global climate burden associated with food supply, and may exacerbate concerns over future food security, especially in a warming climate. Moreover, keeping people warm in winter may reduce cold temperature-related mortality. Hence, the balance between heating/cooling our environment to keep TEE stable or pushing those costs onto the individual has diverse and complex consequences.

However, what is clear at the moment is that we are literally destroying the planet so we can stay comfortable in our living spaces. Relatively small changes in the temperatures at which we regulate our homes can have big impacts on building energy use, with minimal impacts on comfort, because they can be ameliorated by using our second unique capacity with respect to themoregulation: that is, the ability to rapidly adjust our external insulation (clothing).

And, if we decide not to make such clothing adjustments, that may – in the end – be the easiest strategy of all to activate BAT and treat obesity. Impacting two of the biggest current issues on the planet (obesity and climate change) may be as simple as turning down the thermostat dial in your living room!

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POLYCYSTIC OVARY SYNDROME: THE HUNT FOR NEW THERAPIES

WRITTEN BY MICHAEL W O'REILLY

Clinical, mechanistic and societal awareness of polycystic ovary syndrome (PCOS) is steadily improving. However, our quest for novel therapeutic options needs to accelerate.

Debate in relation to the diagnostic criteria for PCOS has raged for over three decades. Most international consensus groups agree that the cardinal clinical features are oligomenorrhoea coupled with clinical or biochemical evidence of androgen excess. Awareness of the long term metabolic health complications of PCOS has increased significantly in recent years.

PCOS-related health costs in the USA were estimated at a staggering $8 billion in 2020,[1] with between 7% and 17% of all women affected, depending on the diagnostic criteria applied. However, PCOS consistently receives relatively paltry National Institute for Health and Care Research funding, which is dwarfed by that allocated to many other chronic diseases.[2] It is also very telling that the first international clinical practice guideline for PCOS was only published in 2018.[3]

PATHOPHYSIOLOGY AND HEALTH CONSEQUENCES

Androgen excess is one of the central pathophysiological features of PCOS. Its pathogenesis reflects a complex interplay between insulin resistance and androgen metabolism, with hyperinsulinaemia driving androgen generation at the level of the ovary, adrenal and adipose tissue.[4] Whilst not included in diagnostic criteria, up to 75% of women with PCOS demonstrate features of insulin resistance.[5] Androgen excess and insulin resistance together underpin the metabolic perturbations observed in PCOS.

Women with PCOS have a two- to fourfold increased risk of developing type 2 diabetes mellitus over the course of their lifespan, compared with the matched background population.[6] Higher incidence rates of ischaemic heart disease, obstructive sleep apnoea and non-alcoholic fatty liver disease have been reported in multiple studies. A retrospective cohort study of 176,000 women with PCOS in the Clinical Practice Research Datalink dataset demonstrated a 26% increase in non-fatal myocardial infarction, revascularisation and angina.[7]

Long term health consequences of PCOS are not limited to metabolic dysfunction and subfertility. Higher rates of mental health disorders and reduced quality of life are regularly reported by women with PCOS. Adverse neurodevelopmental outcomes appear to be increased in children born to women with PCOS, including higher rates of autism spectrum disorder and attention deficit hyperactivity disorder.[8] A recent study from the North Finland Birth Cohort found that women with PCOS had a lower potential to remain in permanent employment by the age of 46, gaining on average 30 additional disability and unemployment days compared with controls over the course of their working careers.[9]

A HIDDEN HEALTH EPIDEMIC

Clearly many patients with PCOS have a mild clinical phenotype and do not require any specific health interventions. The cohort of patients who attend our endocrinology and gynaecology clinics are likely to represent the more severe end of the phenotypic spectrum. However, the sheer scale of prevalence of PCOS in the background population, with 50% of patients remaining undiagnosed, means that there is a hidden health epidemic grumbling below the radar of mainstream health surveillance.

'The sheer scale of prevalence of PCOS in the background population means that there is a hidden health epidemic grumbling below the radar of mainstream health surveillance.'

The clinical features of PCOS are closely entwined with obesity in up to 70% of patients; severity of androgen excess, metabolic dysfunction and oligomenorrhoea are all exacerbated by weight. This relationship between PCOS and weight is highly complex and likely to be bidirectional. As our societal struggle with overweight and obesity intensifies, with sobering predictions for the coming decades, it is inevitable that PCOS-related health complications will continue to pose huge healthcare challenges.

MANAGEMENT OPTIONS

The obvious question to ask at this point is whether anything can be done to normalise or reduce health risks in such a complex and heterogeneous population? At present, there are no disease-specific therapies to mitigate metabolic risk for women with PCOS. We have repurposed drugs like metformin to increase ovulation rates, but there is no evidence that this prevents long term metabolic health complications. The combined oral contraceptive pill is widely prescribed for cycle regulation and anti-androgenic impact,[7] but it is relatively contraindicated in patients with obesity who are at the greatest risk of metabolic complications.

Are pharmacological weight loss interventions with novel therapies like glucagon-like peptide-1 (GLP-1) analogues or the highly promising GLP-1/glucose-dependent insulinotrophic polypeptide agonists one potential solution? Possibly, yes – however, up to 30% of women with PCOS are neither overweight nor obese, so focusing exclusively on weight loss would be an oversimplification of the problem.

Increasing evidence suggests that androgen excess plays a causal role in many of the health-related complications in PCOS. Prenatal androgen exposure in rodent and non-human primate models is consistently associated with glucose dysregulation in female offspring, and androgen exposure *in vivo* and *ex vivo* is associated with adipose tissue dysfunction in women.[4]

A logical next step should be to explore the impact of highly selective androgen receptor antagonists, or inhibitors of androgen activation, on carbohydrate and lipid metabolism in women with PCOS. There will be significant challenges to the design and conduct of clinical trials of these medications in women of reproductive age. However, this area is consistently identified by patient support groups for PCOS as their primary desired research objective. Progress to date has been too laborious, but it is now time to start listening to our patients.

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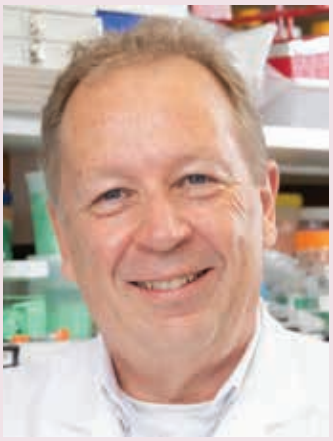

Philipp Scherer is Professor and Director of the Touchstone Diabetes Center at the University of Texas Southwestern Medical Center in Dallas, TX, USA. Throughout his career, he has maintained an interest in processes related to cellular and systemic energy homeostasis, with a special focus on the adipocyte. He identified adiponectin, one of the first secretory factors to be described that almost exclusively originate in adipose tissue.

He presented his Transatlantic Medal Lecture 'Adipose tissue organ crosstalk in health and disease' at SfE BES 2022. We caught up with him to learn more about his career, research and academic inspiration.

Tell us about your career so far

I was born and raised in Switzerland, and ended up undertaking my PhD in biochemistry at the University of Basel. I then moved on to the Whitehead Institute at Massachusetts Institute of Technology as a postdoc, before accepting a faculty appointment at the Albert Einstein College of Medicine in New York. I was there for 10 years and built a programme in the area of adipose tissue physiology.

In 2007, I joined the University of Texas Southwestern Medical Center as the head of the Touchstone Diabetes Center. Here, my primary focus is on adipose tissue, biology and physiology, and how this fits into the bigger picture of a number of pathophysiological states, including diabetes. I've now been there for 15 years, and try to carry the heritage of the Swiss mountains with me to the flatlands of Dallas and the heat of the southwest USA.

How has the study of diabetes changed?

We have definitely moved into the era of omics large-scale generation of data at every level, which includes a lot of data from preclinical models and is our strength. Mouse genetics, and how we analyse these mice, have also made major technological leaps forward. Recently, we developed high spatial resolution, in terms of actually applying these omics technologies to relatively small, defined areas within tissue, even down to the level of the single cell. That has been quite the game changer, in terms of how we approach the disease state at many different levels.

What achievements are you most proud of, so far?

I've certainly contributed to some key findings, including a number of molecules that are considered important in our field. One of those molecules is adiponectin. Another that's becoming rapidly more 'popular' is endotrophin. In my area of research, we take pride in the fact that we've hopefully managed to put the fat cell 'centre stage' as an endocrine cell and defined its interactions with other cell and organ types.

In academia, I also take pride in my academic offspring, including the ability to place many of my trainees in tenure-track positions at universities, or to see them flourish in a pharmaceutical or biotech environment. That's a legacy that I'm very proud of.

Who has had the biggest impact on your career?

Mentors, during the early stages of your career, play a major role. I was mentored in my PhD by Gottfried Schatz, renowned for his contributions in defining the biogenesis of mitochondria. My postdoctoral mentor, Harvey Lodish from the Whitehead Institute, brought the adipocyte to my attention as an interesting cell type. I certainly learned a lot from Harvey, not only about the science, but also in terms of running a scientific programme. This included growing a lab, and managing all the different demands you face day-to-day when you have a large number of people working around you. Those are the two key people from the formative years of my career that had a great impact.

I've also profited a great deal from my colleagues at the Albert Einstein College including, amongst many others, Michael Brownlee and Luciano Rossetti, who both contributed significantly to my career development. The field of metabolism is great to work in, with a lot of good people and a healthy competitive environment.

What are the biggest challenges in your field?

We have a lot of unsolved problems. We are 100 years beyond the discovery of insulin, yet we haven't cured diabetes per se. Major leaps have been made, but many big questions remain concerning the set points for our adiposity.

We always say that adipose tissue distribution is like real estate. It's all about location, location, location. So, how do we funnel specific, excess calories to specific fat parts? It's still, at this point, not possible through directed intervention. We have to find out how we can direct these calories into specific fat pads.

The holy grail of adipose tissue research is how to learn more about fat as a signalling entity. How is the initial set point for adiposity established and maintained in a way that the body returns to its maximal adiposity, even after pharmacological intervention, which can see 20–25% weight loss?

What was the focus of your lecture at SfE BES 2022?

I emphasised the endocrine role of adipose tissue and its multifaceted actions in influencing both the local microenvironment and cross-communication with a range of other organ systems. We still have so much to learn about adipose tissue-derived communication. Fat is one of our major endocrine organs in terms of size and absolute amount. So, I tried to share some of the excitement that is developing in the field around the multiple aspects of adipose tissue physiology and endocrinology.

What are your words of wisdom for future endocrinologists?

We still have a lot of problems to solve, which ultimately means this is a research area that it's worth getting into. Particularly as an endocrinologist, you're at the interface between the clinic and the bench, where you can address issues more mechanistically. It's a rapidly evolving and exciting field. There is a very broad set of techniques that we can apply to our research, so it's never going to be boring. I recommend getting into the field and interacting with key people. I hope we can continue to recruit talented people into the areas of metabolism and endocrinology.

Society for Endocrinology

Clinical Resource HUB

Giving you the tools to help transform patient care

This Hub will give you the tools you need to help innovate clinical service delivery.

You can find resources such as:

- Patient initiated follow-up (PIFU) guidance
- Job planning
- Clinical pathways
- Patient information sheets
- The full Defining the Future of Endocrinology report and its recommendations

Help us grow this Hub by submitting a resource. Get in touch on clinical@endocrinology.org

SCAN ME

SfE BES 2022 IN PHOTOS

Our annual Society for Endocrinology BES conference was held in Harrogate on 14–16 November. The event attracted over 1,200 attendees for three days of the very best clinical and scientific endocrine research from across our discipline.

It was fantastic to see attendance back to levels seen before the COVID-19 pandemic, with a buzzing conference bringing our community together to learn from each other, share their passion and collectively work towards advancing research and improving patient care.

Several sessions are now available to watch on demand.

Here's a selection of our photo highlights, including plenary lecturers, welcome drinks, Early Career Curry and Quiz, the conference dinner and the prizes and awards session.

We thank all our exhibitors and sponsors for supporting this amazing event and hope to see you all at SfE BES 2023!

REWARDING EXCELLENCE

It's not all about the prestigious Medal Lecturers at the SfE BES conference, the best presentations on new research and clinical practice advances were also recognised with a selection of prizes awarded at the event.

ENDOCRINE NETWORK PRIZES

Best Oral – Adrenal and Cardiovascular: Kerri Devine (OC4.3)
Best Poster – Adrenal and Cardiovascular: Emily Goodchild (OP2.3)

Best Oral – Bone and Calcium: Kreepa Kooblall (OC1.6)
Best Poster – Bone and Calcium: Nicole Ball (OP5.1)

Best Oral – Endocrine Cancer and Late Effects: Selvambigai Manivannan (OC2.2)
Best Poster – Endocrine Cancer and Late Effects: Sruthi Murthy (OP6.4)

Best Oral – Metabolism, Obesity and Diabetes: David Dearlove (OC5.5)
Best Poster – Metabolism, Obesity and Diabetes: Annabelle Milner (OP4.2)

Best Oral – Reproductive and Neuroendocrinology: Layla Thurston (OC3.6)
Best Poster – Reproductive and Neuroendocrinology: Edouard Mills (OP3.1)

Best Oral – Thyroid: Ling Zha (OC6.2)
Best Poster – Thyroid: Ali Khalid (OP1.1)

CLINICAL ENDOCRINOLOGY TRUST PRIZES

Best Basic Abstract: Aanya Hirdaramani (EC1.4)
Best Clinical Abstract: Peter Taylor (EC1.3)
Best Nursing Practice Abstract: Claire Stirling (P149)

ANNETTE LOUISE SEAL AWARD

Sponsored by the Addison's Disease Self-Help Group
Lisa Shepherd (P150)

FEATURED CLINICAL CASES POSTER PRIZE

Supported by Endocrinology, Diabetes and Metabolism Case Reports
Kieran Mistry (CC3)

SfE BES GLASGOW 2023

SAVE THE DATE

Society for Endocrinology BES 2023
Glasgow, UK, 13–15 November
www.endocrinology.org/sfebes-2023

SEVERE HYPERTRIGLYCERIDAEMIA AND CHYLOMICRONAEMIA

WRITTEN BY BILAL BASHIR AND HANDREAN SORAN

Triglycerides form the major component of dietary fat. They are hydrolysed by lingual, gastric, pancreatic and intestinal lipases into free fatty acids (FFA) and glycerol, which are re-esterified to triglycerides in enterocytes and packaged into the transport cargo, chylomicrons. Chylomicrons are hydrolysed by lipoprotein lipase (LPL), which is expressed at high concentration on the capillary surfaces of muscle and adipose tissue.

TRIGLYCERIDES AND SEVERE HYPERTRIGLYCERIDAEMIA

Definition of severity of hypertriglyceridaemia varies amongst different guidelines. However, normal levels of fasting triglycerides have consistently been described as <1.7mmol/l. The 2018 American Heart Association/American College of Cardiology Clinical Practice Guidelines and US National Cholesterol Education Programme Adult Treatment Panel III Guidelines have defined severe hypertriglyceridaemia as >5.6mmol/l, while the Endocrine Society and the European Atherosclerosis Society/European Society of Cardiology have defined this as >10.0mmol/l.[1–4]

Severe hypertriglyceridaemia is rare and is associated with genetic polymorphism that is often exacerbated by environmental factors. There are more than 300 independent gene loci that can affect plasma triglyceride levels with variable effect size. A single, extremely rare variant with a large effect size can lead to severe hypertriglyceridaemia (e.g. monogenic familial chylomicronaemia syndrome; FCS). An increase in mutational load of common variants with small effect size, compounded by environment factors, can cumulatively increase triglyceride levels (multifactorial chylomicronaemia syndrome; MCS).[5–6]

WHAT IS CHYLOMICRONAEMIA SYNDROME?

Chylomicronaemia is persistence of chylomicron particles in the circulation after a fasting period of 12–14 hours (they are normally cleared in 3–4 hours after a meal). This is associated with severe hypertriglyceridaemia (>10.0mmol/l). Chylomicronaemia syndrome is the presence of clinical abnormalities, such as eruptive xanthomas, lipaemia retinalis, recurrent abdominal pain, acute pancreatitis, hepatosplenomegaly, and neuropsychiatric or cognitive complications.

Monogenic causes of chylomicronaemia are extremely rare, with a population prevalence of 1–2 per million.[7] The disease presents in childhood or early adolescence at the latest, and is characterised by severe hypertriglyceridaemia and recurrent episodes of pancreatitis, and is resistant to treatment. These are autosomal recessive disorders and characterised by a marked reduction in LPL activity, either due to mutation in the LPL gene or genes encoding proteins responsible for maturation, stabilisation, transport, anchoring and activation of LPL.

Most cases of chylomicronaemia are polygenic, due to the clustering of multiple genetic variants. An aggravating factor is usually required to augment the metabolic defect to reduce the clearance of chylomicrons. When enough of these variants are cumulatively inherited, they create a tendency to develop chylomicronaemia.[5] In contrast to FCS, MCS has a population prevalence of 1:600, a milder phenotype and a relatively low risk of acute pancreatitis. It is generally more responsive to treatment or removal of secondary factors and lipid-lowering medications.

Metabolic phenotypes of FCS and MCS largely overlap, particularly during the periods of decompensation. The diagnosis of FCS is delayed in most patients, who suffer multiple attacks of acute pancreatitis before a diagnosis of FCS is made. While the gold standard to diagnose FCS remains genetic testing, the pre-test probability of FCS is evaluated by an eight-item scoring system, where a score of ≥10 yields a sensitivity of 88% and a specificity of 85% (Figure).[8]

ACUTE PANCREATITIS AND SEVERE HYPERTRIGLYCERIDAEMIA

Acute pancreatitis is the most serious complication of severe hypertriglyceridaemia, and its prevalence increases sharply if the level of triglycerides is >20mmol/l. Hypertriglyceridaemia constitutes only 5% of cases of acute pancreatitis, but it is associated with a more severe disease course, persistent organ failure, higher recurrence rate, greater length of hospital and intensive care unit stay and increased severity of complications and mortality when compared with other causes of acute pancreatitis.[9]

Although there is no correlation between severity of acute pancreatitis and severity of hypertriglyceridaemia, the disease course, recurrence and complications tend to be higher in FCS when compared with MCS.

Figure. The pre-test probability of FCS is evaluated by an eight-item scoring system, where a score of ≥10 yields a sensitivity of 88% and a specificity of 85%.[8] [a]Plasma triglyceride (TG) concentrations measured at intervals of at least one month. [b]Secondary factors include alcohol, diabetes, metabolic syndrome, hypothyroidism, corticosteroid therapy and additional drugs.

1. Fasting TGs >10mmol/l for three consecutive blood analyses[a] [+5]
   Fasting TGs >20mmol/l at least once [+1]
2. Previous TGs <2mmol/l [−5]
3. No secondary factors[b] except pregnancy or ethinyloestradiol [+2]
4. History of pancreatitis [+1]
5. Unexplained recurrent abdominal pain [+1]
6. No history of familial combined hyperlipidaemia [+1]
7. No response (TG decrease <20%) to hyperlipidaemic treatment [+1]
8. Onset of symptoms at age:
   <40 years [+1]
   <20 years [+2]
   <10 years [+3]

FCS score
≥10: FCS very likely
≤9: FCS unlikely
≤8: FCS very unlikely

Table. Novel triglyceride (TG)-lowering agents that target LPL and its regulators are in various phases of development. EMA, European Medicines Agency; MTP, microsomal triglyceride transfer protein.

Drug	Effect on TG	Phase of development
Volanesorsen	50–70% reduction	Approved by EMA for use in FCS in 2019 Approved by NICE for use in FCS in 2020
Olezarcen	70% reduction	Phase III trial expected to be completed in 2025
Evinacumab	55% reduction	Phase II trial for severe hypertriglyceridaemia and acute pancreatitis expected to be completed in 2024
ARO-APO CIII	40–70% reduction	Phase II trial is expected to be completed in December 2023
ARO-ANG3	Up to 66% reduction	Phase II trial is expected to be completed in 2023
STT-5058	–	Phase I trial was scheduled to be completed in November 2022
Lomitapide	MTP inhibitor	Approved by EMA in 2013 for homozygous familial hypercholesterolaemia Two case reports of FCS managed with lomitapide with >50% reduction in TG and elimination of further episodes of acute pancreatitis but risk of liver fibrosis
Pradigastat	40% reduction	No updates since 2015
Other, suspended therapies		
Alipogene tiparvovec (Glybera)	40–60% reduction	Approved by EMA in 2012 for clinical use but withdrawn from the market owing to poor commercial prospects in 2017
Vupanorsen	50–60% reduction	Development halted in 2022 after a review of phase 2b (TRANSLATE-TIMI) study

There are no universally accepted guidelines for the management of hypertriglyceridaemia-induced pancreatitis and no realistic goals have been established. The probability of developing persistent organ failure can be reduced by rapidly reducing the triglyceride levels to <5.6mmol/l within the first 48 hours. This effect is time-sensitive, i.e. the earlier the goal is achieved the lower the likelihood of developing persistent organ failure.[10]

'There are more than 300 independent gene loci that can affect plasma triglyceride levels with variable effect size.'

THERAPEUTIC OPTIONS IN ACUTE PANCREATITIS

Half of the mortality from acute pancreatitis happens within two weeks from the onset of symptoms. Bowel rest, intravenous hydration, pain management, restricted oral intake, low fat diet (<20g/day) and avoidance of oil-based medication (e.g. propofol) remain the key therapeutic interventions that should be employed as soon as the diagnosis is suspected.

Intravenous insulin infusion reduces triglyceride levels by up to 75%, by upregulating LPL activity. This may reduce the severity of pancreatitis, hasten the recovery and reduce the hospital stay. Intravenous heparin infusion reduces triglyceride levels early but, due to the risk of rebound hypertriglyceridaemia, worsening lipotoxicity from FFA and pancreatic haemorrhage, it is not recommended.

Lipoprotein and plasma apheresis not only remove chylomicrons and triglycerides rapidly from the circulation, they also remove proinflammatory cytokines to downregulate the inflammatory process in hypertriglyceridaemia-induced pancreatitis.[11] Despite that, it has failed to demonstrate a reduction in morbidity or mortality, and is recommended only in individual cases who fail to improve despite conservative treatment, under specialist advice.

Of the pharmacological agents that are currently available, the lipid-lowering efficacy of fibrates, niacin and omega-3 fatty acids in chylomicronaemia syndromes is modest at best, with no effect on triglyceride levels in FCS. Several novel triglyceride-lowering agents that target LPL and its regulators are in various phases of development (Table). Volanesorsen was approved by NICE in 2020 as a therapeutic option for individuals with genetically confirmed FCS who are at risk of pancreatitis. It reduces serum triglyceride levels by 70–80% and the risk of recurrent pancreatitis. Thrombocytopenia remains a predominant concern with volanesorsen, requiring regular monitoring every one to two weeks. It is not advisable to start treatment if the platelet count is $<140x10^9$/l. No other drug has yet been approved for standard clinical use.

Chylomicronaemia syndromes pose a major clinical burden with potential to develop life-threatening pancreatitis. At present, low fat or fat-free diet and lifestyle modifications continue to be the cornerstone in the management of these syndromes, but are often difficult to adhere to. Novel therapeutic targets (Table) may offer solutions for their treatment and the prevention of associated complications.

BILAL BASHIR AND HANDREAN SORAN
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WHAT IT MEANS TO BE A CONSULTANT GENETIC COUNSELLOR

Melanie Watson is Consultant (Lead) Genetic Counsellor at Wessex Clinical Genetics Service, and Lead for the Wessex Familial Hypercholesterolaemia Service, based in Southampton and working across the Wessex region. This service was launched in July 2014 and has been fully commissioned since July 2016. We talked to her about what she undertakes in the course of her job.

What is involved in your role?

We are at the dawn of a genomics era within the NHS. In my post, I am responsible for the clinical leadership, education and training, and research and development of the Wessex Familial Hypercholesterolaemia Service. This offers genomics and cascade genetic testing to individuals and families affected by this condition.

What does clinical leadership entail?

As a clinical lead, I anticipate and respond to the changing demands on this service. I ensure that the service, and the nurses who work in familial hypercholesterolaemia, have the capacity and support they need to provide a patient- and family-centred approach to genomic testing for the condition. In recent months, a number of external factors have changed the way in which the service has been delivered.

For instance, the COVID pandemic meant that the nurses were temporarily redeployed to the frontline. This required the familial hypercholesterolaemia service to be temporarily suspended. On its relaunch, we provided consultation on a virtual platform to address the restrictions of the pandemic.

> *'As we look to the future and hopefully identify individuals with familial hypercholesterolaemia at a younger age, it will be important to monitor the clinical effectiveness, acceptability and cost-effectiveness of treatment in this age group.'*

The 'additional findings' from the 100,000 Genomes Project have also had an impact.[1] As part of participants' consent for the 100,000 Genomes Project, they were asked if they wanted us to look for additional health information in their genome sequence (called 'additional findings'). They were informed that 'these conditions could be serious, but the NHS can already treat them or use screening to pick them up at the earliest stage possible'. Familial hypercholesterolaemia was included in this group of conditions. Although the patients gave consent, the realisation that they were affected by another genomic condition was sometimes a challenging path to navigate for both individuals and families.

Finally, with the clinical introduction of new treatments such as PCSK9 inhibitors, the service has had to respond by establishing PCSK9 clinics to monitor and support the implementation of these treatments with a genomic basis.

How have you been involved in education and training?

The NHS Long Term Plan[2] was introduced in January 2019, to expand access to genetic testing for familial hypercholesterolaemia, with the aim to improve identification from 7% to 25% in the next five years. Alongside this, a National Education Programme (NEP) for familial hypercholesterolaemia was launched. As a member of this NEP group, I helped develop the competency framework for familial hypercholesterolaemia and mapped a training and education programme against these competencies, delivering a national workshop.

This work is ongoing, with the development of Massive Open Online Courses to future-proof this programme.

At a regional level, the Hampshire and Isle of Wight Integrated Care Board (ICB) has responded to the new Directed Enhanced Service (DES) Indicators for familial hypercholesterolaemia, with the aim of increasing the identification of the disease in primary care. I worked proactively with the ICB and the Academic Healthcare Science Network to develop an intervention brief incorporating a clinical pathway to respond to this DES to identify familial hypercholesterolaemia in primary care. This has been supported by educational webinars for GPs and allied healthcare professionals who have a role to play in this primary care clinical pathway.

Tell us about your role in research and development

When establishing this service, it was important to engage with key stakeholders to develop sound economic modelling, ensuring its sustainability.[3] This work is ongoing as the commissioning structures change.[4] It has been subject to a National Institute for Health and Care Research Health Technology Assessment, to investigate the cost effectiveness of cascade testing for familial hypercholesterolaemia in primary care, soon to be published.

As we look to the future and hopefully identify individuals with familial hypercholesterolaemia at a younger age (in childhood), it will be important to monitor the clinical effectiveness, acceptability and cost-effectiveness of treatment in this age group, and also to ensure the training and support of paediatric endocrinologists to provide this treatment and care.

It is a privilege to help steer this service into the genomics era, and to have such a multifaceted role as a Consultant Genetic Counsellor for familial hypercholesterolaemia.

MELANIE WATSON
Consultant (Lead) Genetic Counsellor, Wessex Clinical Genetics Service, and Lead, Wessex Familial Hypercholesterolaemia Service, Southampton

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Obesity and type 2 diabetes: TIME TO PUT AWAY THE KNIVES?

Society for Endocrinology METABOLIC AND OBESITY

UPDATE FROM THE SOCIETY'S METABOLIC AND OBESITY ENDOCRINE NETWORK

So it's official: obesity is now recognised as a complex chronic disease with significant morbidity and mortality. One of its main metabolic complications is type 2 diabetes, and the two conditions share key pathophysiological mechanisms. The diagnosis of obesity is, however, complex, and one size does not fit all.

A CHANGE OF LIFESTYLE?

Lifestyle interventions can be impressive, as evidenced in the DiRECT trial. After two years of follow-up in the intervention arm, where participants received a very low calorie diet (an 825–853kcal/day formula diet for three to five months), followed by food reintroduction and structured support for weight loss maintenance, 11% of participants lost ≥15kg and overall diabetes remission at two years was 36.5%.

Typically, most lifestyle interventions result in progressive weight loss over six months, followed by plateau and weight regain over a period of one to three years. The need for obesity management services to enable long term support of these individuals with lifestyle counselling and access to relevant multidisciplinary teams is clear.

'Although it appeared that the surgeons were sharpening their knives and taking centre stage in the management of the condition, it wasn't quite time for the endocrinologists to exit.'

THE ROLE OF SURGERY

Surgical weight loss beats diet and exercise for reversing diabetes. The impact of gastric bypass surgery in most randomised controlled trials typically results in a 20–25% decrease in body weight, which is sustained with improvements in metabolic control. More importantly, the extensive experience with bariatric/metabolic weight loss shows that this sustained reduction in weight leads to reduced mortality and morbidity, for example from cardiovascular disease, and surgery is highly cost-effective.

Although it appeared that the surgeons were sharpening their knives and taking centre stage in the management of the condition, it wasn't quite time for the endocrinologists to exit. Post-bariatric hypoglycaemia was recognised to be a major side effect. Symptomatic hypoglycaemia may be experienced by one person in three, but severe hypoglycaemia (which can be life-threatening with altered consciousness) may be experienced by one in a hundred.

This side effect is a serious problem, affecting patients' ability to work or drive, and causing psychological damage. No guidelines exist, and the evidence base for management is relatively small. Advice with respect to driving licensure and the use of glucose monitors across the country is inconsistent.

The Society's Metabolic and Obesity Endocrine Network has been working hard to solve this, by drawing up a set of consensus guidelines.

MEDICAL INTERVENTION

We now live in interesting times for the medical treatment of obesity. Recent data from trials of the high dose glucagon-like peptide-1 (GLP-1) analogue semaglutide and the novel glucose-dependent insulinotrophic polypeptide/GLP-1 receptor agonist tirzepatide suggest that people with obesity can lose between 15–20% body weight. Is it now time for a rethink?

Although these are impressive headline figures, the limited length of the trials for these agents and the cumulative high cost will mean that they can only be employed for relatively short periods of time (e.g. two years for high dose semaglutide), and in limited populations defined by high body mass index and the presence of co-morbidities. Moreover, it is presently unclear whether these new treatments will have a significant impact on the co-morbidities of obesity and overall mortality. Early data on liver fat clearance with tirzepatide are promising and being fully evaluated in the SYNERGY trial.

WHAT NEXT?

So is it now time to put away the knives? We argue that both surgery and the newer drugs will have their place in the management of obesity.

However, a serious effort to prevent the development of obesity in childhood is required, to head off the tsunami of obesity which we face, and the clear socioeconomic inequalities of this disease. The 'obesogenic' food environment does not support those on lower incomes to choose healthy diets. The prevalence of obesity in children from deprived areas in the UK is 20% among those at reception age, approximately double that seen in children from more affluent areas. Affordability, availability and the marketing of less healthy food and drink products all contribute.

The Soft Drinks Industry Levy has shown that legislation can make a small difference in population sugar consumption, but larger governmental efforts are required to 'move the needle' sufficiently to alter the upwards trajectory of obesity. Which is why the proposed removal of the obesity strategy by the incumbent government is disappointing.

SHAREEN FORBES
University of Edinburgh

TRICIA TAN
Imperial College London

GAVIN BEWICK
King's College London

Shareen Forbes and Gavin Bewick are the Clinical and Science Convenors for the Society's Metabolic and Obesity Endocrine Network. Post-bariatric hypoglycaemia guidelines are currently being drawn up by the multidisciplinary Metabolic and Obesity Endocrine Network working group.

Changing faces OF THE SOCIETY

Our Council and Committees form the decision-making structure for the Society. These groups of members ensure that the Society is supporting its members and the field of endocrinology in the best possible way. This is done by reflecting on the external challenges that you all face and considering how the Society can best support you.

DIVERSITY IS KEY

The members who belong to our Society are found in many different institutions, working different job plans, holding different experience, and from different backgrounds. All have slightly (or very!) different perspectives on how the Society can best support endocrinology. Post-pandemic, our members are facing new and different challenges that the Society needs to understand better.

This diversity and pace of change mean we need many different voices to be represented in the Society's leadership – on Council and on our Committees. This will ensure we can evolve and adapt to support endocrinology, both now and into the future.

There's also a lot to gain individually by taking on one of these roles. Members get the chance to expand their own professional network and have the opportunity to use skills in new ways – as well as to shape the work of the Society.

HOW WE'VE CHANGED OUR PROCESS IN 2022

Our recent governance review made it clear that the Society needs to be more transparent about the process for electing members into key positions. While examining how best to do this, we've made additional changes, in order to make our processes more robust and more inclusive.

The principle we are following is that **governance roles within the Society should be openly advertised and recruited for based on skills and motivation.**

This year our role descriptions have been updated with a more accurate description of responsibilities, together with required skills for each role. Our application forms have been updated (and renamed from 'nomination' forms), and streamlined to focus on motivation and evidence of skills for roles, rather than asking for biographies, as previously.

Committee Chair positions will now be applied for, rather than being decided by the Nominations Committee. These positions, in addition to Council positions, will go out to the membership for a vote if there are more applications than vacancies. Importantly, this ensures that our members have a say in who is representing them.

We're also working harder to **raise awareness** of our vacancies, the process, and our need for wide representation and diversity within the Society's governance. We hope this will encourage new faces to apply for Society roles.

Read the full review of the Society's governance structures and processes with recommendations at **www.endocrinology.org/gov-review**.

2023 ELECTIONS: KEY STATS

2 MEMBER VOTES

were held: one for the Public Engagement Committee Chair and the other for who should fill the four Council member vacancies.

A total of **67 APPLICATIONS** were received for **50 VACANCIES** (an average of 1.34 applications for each position). In previous years we have often struggled to fill vacancies.

Your voice
OUR SOCIETY

CONGRATULATIONS!

We welcome everyone who is taking up a new position after our 2022 AGM:

Professor Márta Korbonits
President

Professor Kristien Boelaert
Clinical Committee Chair

Mrs Louise Breen
Nurse Committee Chair

Dr Niamh Martin
Public Engagement Chair-elect

Dr Zoi Michailidou
Science Committee Chair-elect

NEW COUNCIL MEMBERS:

Dr Miles Levy

Dr Onyebuchi Okosieme

Dr Michael O'Reilly

Dr Helen Simpson

HOW CAN WE IMPROVE FURTHER?

Let us know how we can make our governance processes even better. The Society's Equality, diversity and inclusion working group is currently busy examining governance as well as other Society activities and will make recommendations to Council in 2023. If you have any suggestions, contact **council@endocrinology.org**.

Funded by SOCIETY MEETING SUPPORT GRANTS

Spotlight on physical activity and the endocrine system

Physical activity (PA) is 'any bodily movement produced by skeletal muscles that requires energy expenditure'. Our hormones play an important role in the response to and recovery from PA. For this reason, we decided to organise a focused scientific meeting with support from the Society for Endocrinology.

Read abstracts of the prize-winning oral presentations from the meeting at **www.endocrinology blog.org**.

IMPORTANT INTERPLAY

Despite the important interplay between PA and the endocrine system, our experience within a sport and exercise science department is that many researchers within our field would rarely deem themselves to be researching aspects of endocrinology. This is the case even though they analyse a wide range of hormones, cytokines and other chemical messengers regularly within their experiments. Likewise, endocrinologists would very rarely think of themselves as having overlapping links with PA and sport and exercise sciences research.

As members of the Society for a number of years, and being involved in the Early Career Steering Group, in governance reviews and in judging undergraduate members' video competitions, we rarely crossed paths with fellow researchers in sport and exercise sciences. Nor is it apparent within the annual Society for Endocrinology BES conference that there is a clear section in which these overlapping themes could fit.

It was for these reasons that we wanted to create an event to highlight PA and endocrine research. The primary aim of applying for the Society's Meeting Support Grant was to acquire support to stage such an event. We wanted the event to be inclusive and accessible to all and therefore decided to hold a free event with the support of the Society.

PURSUING OUR VENTURE

We took our first steps in 2021: we were awarded a Meeting Support Grant which allowed us to host a two-day virtual conference. With the help of the Bioscientifica events team, we planned and prepared for the conference over the course of six months. Pursuing this venture was a new experience for both of us, and we were extremely grateful for the support we received from both Bioscientifica and the Society, which helped to create a professional and interesting conference.

Over the course of the two-day programme, an average of 80 people tuned into our talks at any one point. We had 16 oral communications from early career researchers, giving each a chance to present within a friendly environment. After such a successful event, we even had an offer to make this a commercial venture, something we are still mulling over!

OUR SECOND EVENT

Building on our success in 2021, we were determined to host an in-person event. Another successful Meeting Support Grant application to the Society gave us the capital we needed to fulfil this aim.

The event was hosted in July 2022 at Nottingham Trent University (NTU)'s Clifton Campus and attracted over 100 registrants, with around 85 people attending on the day. It not only attracted experienced researchers to NTU, it also gave an opportunity for early career researchers from across the country to submit their work and present to an engaged and friendly audience. We hosted speakers from the USA, Canada and the UK.

CHALLENGES AND SUCCESSES

Our experience of organising and hosting Society-supported conferences at NTU over the past two years has been positive. Enlisting the expertise and support of the Bioscientifica events team for our virtual conference and our own in-house events team for our face-to-face conference at NTU resulted in the creation of professional, well organised events.

> *'It was very satisfying to be able to make our events free and accessible to all.'*

The challenges we faced for both events were budget and event management, and the balancing of these new tasks alongside our own daily workloads. This year, with a face-to-face event, we needed to provide a stimulating environment and a warm welcome to all our attendees at our NTU campus. The first and perhaps the most important task in creating this environment was the development of the scientific programme.

We designed a wide-ranging programme, focusing on the effect of PA on energy balance and cellular metabolism. We also developed an expert panel session, focusing on sex differences in PA and endocrine research. We committed to inviting world-leading researchers in these areas, with a mixture of early career and established researchers in their fields. We were delighted to succeed in attracting a group of national and international world-leading researchers for this year's event.

With the scientific programme in place, the event itself needed detailed planning. The main challenge we faced was planning our budget without knowing the number of attendees. Fortunately, the experience of our virtual conference in 2021 enabled us to estimate attendee numbers well.

REFLECTING ON OUR EXPERIENCE

Overall, we have been able to run two successful conferences with the support of the Society. We have gained invaluable personal experience in the creation and management of these events and are proud to have provided opportunities to many early career researchers to present in a friendly and engaged environment. It was very satisfying to be able to make our events free and accessible to all.

We wish to continue with a face-to-face conference in 2023 which we hope will be supported by the Society, and we look forward to welcoming Society members to our event.

JOHN HOUGH AND JESSICA PIASECKI
Senior Lecturers in Exercise Physiology,
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Inspiring early career endocrinologists at EPIC 2022

The starting point was a shared vision of the need for a space for young clinicians and researchers to exhibit their work in research, clinical experience and other aspects of healthcare, among their contemporaries. From this idea was borne the Early Physicians and Investigators Conference (EPIC), which took place on 16–17 July 2022 in Birmingham. As the Local Organising Committee, we are proud to say that we may have even over-achieved, compared with our expectations when we first embarked on this project!

Participants at the 2022 EPIC Meeting.

Supported by a Society for Endocrinology Meeting Support Grant and an Endocrine Ambassador Meeting Grant, this was a two-day event featuring young speakers who ranged from medical students to early career researchers and non-clinical personnel involved in research and development.

With talks on subjects as diverse as adrenal disease management at a molecular level, health economics and neural steroids, it was heartening to see the new generation of researchers showcasing their wares and inspiring others to do the same.

This was also an ideal environment for networking, as evidenced by the presence of members of the Society's Early Career Committee, researchers involved in higher level management of prestigious research establishments and participants from industry.

Feedback from the attendees was positive, with many appreciating the opportunity to present in a relaxed setting. Presentations were scored by moderators in addition to an audience poll. The combined results were used to decided who should receive the award for best presentation. The winner was Manoj Upadhya (Birmingham), who received free registration for the Society for Endocrinology BES conference 2022 in Harrogate.

We hope that EPIC 2022 will be the first of many to come, and that the next meeting will be on a bigger scale with even greater participation. We believe it has the potential to become part of the calendar of essential meetings for future doctors in training and early cwlinical researchers.

PUNITH KEMPEGOWDA, MARK TURNER, ALIYA DALILA RUSLAN, MUNA GUMA, KALYANI NAGARAJAH, VENKATRAM SUBRAMANIAN, KAGABO HIRWA, KERRI DEVINE (now KERRI CHANDLER), ASHMETHAA ASHOKKUMAR, MARIA L PRICE, JESSICA YAU AND RAJEEV RAVI
EPIC Local Organising Committee

YOUR CHANCE TO APPLY

Funds of up to £10,000 are available to help Society members organise events.
Learn more about our Meeting Support Grants and find the next application deadline at **www.endocrinology.org/grants-and-awards**.

Society for Endocrinology

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Nurses' Competency Framework: NEW EDITION GOES DIGITAL

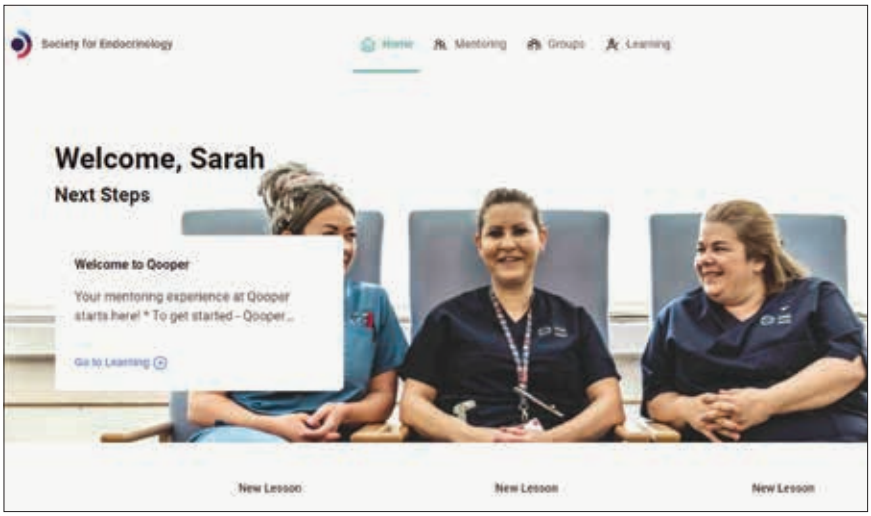
In 2013, the first edition of the *Competency Framework for Adult Endocrine Nursing* was published. It was created by the Society's Nurse Committee in response to an absence of set training in adult nursing for the specialty. Enhanced and republished as the second edition in 2015, not only has this proved immensely valuable in the UK, but it has also been acclaimed worldwide by our endocrine nurse colleagues. It will soon be available in a total of eight languages other than English.

The Nurse Committee has been working on a new edition of the Competency Framework. The levels of experience have been expanded to five, from Novice to Expert. Additionally, a larger number of conditions will be covered.

Following member feedback, this third edition has been created as an online learning platform, to allow nurses to track their progress, access training collateral and, in a new development, connect with more experienced nurses in other centres around the UK. These colleagues will act as mentors and provide support. Initially, it will only be available to members of the Society.

Sandoz has kindly provided funding to support this initiative, which was launched recently at SfE BES 2022.

For more information on how to sign up, email **nurses@endocrinology.org**.



Public engagement through **PLACENTA-THEMED PRINTING**

As a PhD student at the University of Leeds, I am a part of the Forbes and Scott labs, and the Leeds Pregnancy Research Group. Collectively, we investigate healthy pregnancies as well as those affected by gestational disorders, such as diabetes and complications of fetal growth. This research is important because these disorders can lead to increased risk of birth complications and higher likelihood of cardiometabolic disease in later life, for the mother and the offspring.[1,2]

The placenta is a key endocrine organ, which releases hormones to maintain pregnancy and is highly vascularised to allow the transfer of nutrients from the maternal to the fetal circulation to support the growing fetus.[3,4] My research investigates how diabetes in pregnancy can cause the blood vessels in the placenta to develop differently, and how this might be linked to complications for mother and baby.

PUBLIC OUTREACH AND PRINTMAKING

Alongside our research, we regularly take part in public outreach events, to promote awareness of the importance of health during pregnancy, and how this can be a determinant of adult health. Through these experiences, I developed my own activity: 'PlacentArt'. This art activity demonstrates placental blood flow, endocrine function and the vascular structure of the placenta in normal and diabetic pregnancies, through mono- and lino printing.

This stemmed from my own interest in printmaking, which started during a Christmas card lino printing workshop I attended in 2019. I began regularly creating lino prints during the first COVID-19 lockdown in 2020. The subject of these prints was mainly flowers and plants. I opened my own online shop (see **@AbbieByfordPrints** on Instagram) and ran stalls at craft fairs.

ENGAGING THE PUBLIC VIRTUALLY

I planned to conduct the PlacentArt activity at the 2020 University of Leeds Be Curious festival. This annual, open access, free event showcases research across the University through a range of interactive activities, with a target demographic of families.[5] The 2020 event was cancelled due to the lockdown, so I adapted my activity so that it could be done virtually, with items that were easily available at home. I created downloadable materials, including how to monoprint using sandwich bags, paint, paper and cottonwool buds.

A few months later, I worked with the University's Public Engagement Team to send out 10 packs of printing equipment to people in the Leeds area for them to try lino printing. These included placenta factsheets, lino (which was pre-carved with placental structures), printing ink, a printing tray, a roller for the ink, paper, and acetate and pencils for monoprinting. I had support from Rachel Quilang, a post-doctoral researcher in our lab, who helped carve designs into the lino. Alongside this, I created an accompanying demonstration video, which covered the simple and more detailed mono- and lino printing.[6]

Through these virtual events, I adapted my original activity to various printing methods suitable for different age groups. This video and other resources have also been used for other virtual events, including STEM Clubs UK, and the Global Science Show on Twitter.

ENGAGING THE PUBLIC IN PERSON

I have since received a Public Engagement Grant from the Society for Endocrinology, in addition to a grant from the Pathological Society (with Dr Lara Morley), which has allowed me to participate in face-to-face events.

PlacentArt printing packs.

Demonstrating PlacentArt to school pupils at SfE BES 2022 in Harrogate.

In May 2022, the University of Leeds Be Curious festival took place in person again. Around 1,200 people visited the event and 160 staff/students took part. The Leeds Pregnancy Research Group held a stall at this festival entitled 'Womb for improvement'. We conducted a range of activities, including PlacentArt. I pre-carved lino with different placental structures (such as overall structure, cross sections, and diabetic and non-diabetic placentas) prior to the event. These could be used as stamps, for participants to apply ink to and print onto paper.

SfE BES 2022 SCHOOLS OUTREACH EVENT

During the schools outreach event at SfE BES 2022 in Harrogate, three local schools were invited to take part in activities to learn about the world of hormones, and to meet doctors, nurses and scientists.

I was pleased to be invited to conduct PlacentArt at this event. Students were between 14 and 16 years old, which allowed me to explain the cellular structure of the placenta in more detail. I used prints of a placenta cross section and related this to microscopy images of human placentas, which had been generated in our lab. I also highlighted the important role of the placenta in the production of pregnancy hormones, supporting the GCSE curriculum on hormones during reproduction and pregnancy. This also sparked discussions on careers in STEM (science, technology, engineering and mathematics).

EVALUATING THE ACTIVITY

During these events I have collected feedback. I sent an online questionnaire to participants who received printing packs.

Comments showed that they had enjoyed the activity and learned something about the placenta. One person remarked, '[We] loved getting our package through the post – it was like getting a present … I have been meaning to attend the festival in previous years and never quite made it, even though we don't live far from Uni. By having the festival online this year, it has allowed me to attend finally.'

By conducting this activity at both virtual and in-person events, it meant I was able to reach and communicate with more members of the public.

PERSONAL AND PROFESSIONAL GAIN

I have thoroughly enjoyed creating and conducting this activity. Using art has been a great way to enthuse all age groups in science, including children, and to educate them about the placenta and hormones. I also appreciate how much the participants enjoy making the prints.

It has also helped my career development, as I am now a member of the Society for Endocrinology Public Engagement Committee and I been invited to share my experiences at Public Engagement Workshops, including at the SfE BES conference 2020 and the International Federation of Placenta Associations conference 2021.

The Public Engagement Grant from the Society for Endocrinology will enable me to attend future events, in and outside of Leeds, including the Otley Science Festival and Nottingham Festival of Science and Curiosity, as well as Be Curious 2023.

ABIGAIL R BYFORD
BHF 4-year PhD Programme Student, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds

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INTRODUCING THE CLINICAL ENDOCRINOLOGY JOURNAL FOUNDATION

WRITTEN BY GRAHAM LEESE, JOHN NEWELL-PRICE AND HELENA GLEESON

After four decades of support for endocrinology, the Clinical Endocrinology Trust is adopting a new name, to give greater recognition to *Clinical Endocrinology*, the well known journal behind the Trust's success.

A SOURCE OF SUPPORT

Clinical Endocrinology is the official clinical journal of the Society for Endocrinology in the UK and of the Endocrine Society of Australia. The journal works closely with both societies and publishes papers, reviews, commentaries and correspondence which focus on clinical endocrinology practice and science.

The Clinical Endocrinology Trust (CET) was established in 1983, and has supported the activity of mainstream endocrinology in the UK and beyond over the last four decades. It has had ongoing, independent financial support from the journal *Clinical Endocrinology*. This arrangement was originally agreed by the publisher Blackwells, and more recently by Wiley.

We have been surprised how few people realise that the CET has, over the years, been supported by the journal *Clinical Endocrinology*. People have assumed that it is just a trust which supports clinical activity in the field.

Clinical Endocrinology is an official journal of the Society that publishes articles on clinical aspects of endocrinology. Society members can access the journal free of charge online either via the app or by logging in to the Members' Area on the website.

TIME FOR CHANGE

Certainly, in recent years, the journal *Clinical Endocrinology* has thus not received due recognition for its generous, unattributed and independent funding of the Trust and consequent support for activity in endocrinology. In addition, Trust activity has been quiet with COVID and recent reduced opportunities. For all these reasons, and with a new committee appointed, a decision has been made to rebrand and develop the Trust.

After some debate, it has been decided that the new name will be the Clinical Endocrinology Journal Foundation. The remit of the Foundation will be 'to promote clinical endocrinology by supporting research, audit and teaching', which includes quality improvement. The Foundation will continue to be supported by an unattributed award from the journal, and will continue to act independently.

ONGOING SUPPORT FOR ENDOCRINOLOGY

The Clinical Endocrinology Journal Foundation will continue to support education, research, audit and other activities for the betterment of endocrinology and patient care.

The Foundation will still support the Visiting Professor to the British Endocrine Societies. This is a wonderful opportunity for many centres across the UK to hear, first-hand, the knowledge and wisdom of an independent expert. The Foundation will also continue to support an invited speaker at the Society for Endocrinology BES conference, as well as the speaker who delivers the British Thyroid Association Pitt-Rivers Lecture at the same conference.

The Clinical Endocrinology Journal Foundation will give the SfE Skills Academy ongoing financial assistance, as many clinicians worldwide benefit from this. It will also continue to support a lecture at the European Congress of Endocrinology.

Moreover, options for re-establishing other activities, such as small grant schemes, as well as for developing novel exciting opportunities, are currently being explored and will be advertised in due course in *The Endocrinologist* and elsewhere.

GRAHAM LEESE, JOHN NEWELL-PRICE AND HELENA GLEESON
Trustees, Clinical Endocrinology Journal Foundation

RENAMING DIABETES INSIPIDUS

WRITTEN BY MILES LEVY

A position statement outlining the need for changing the name of diabetes insipidus was co-published in several journals on 14 October 2022.[1] This statement was the product of a global, multi-organisational working group, dedicated to improving patient safety and awareness of the condition amongst non-endocrine health professionals. Miles Levy (Leicester), as a member of this working group, tells us more about the case for this important name change.

WHERE IT ALL STARTED – CROYDON 2008

When Malcolm Prentice, a mild-mannered endocrinologist working in South London, contacted us about the terrible case of Kane Gorny, it was impossible not to be moved or not to think that this must never happen again.

The case had achieved notoriety in the media, as Kane rang 999 from a hospital bed after a routine operation. He was not given water to drink or desmopressin. He told the emergency service on the phone he was dying of thirst on the ward, and he was right. The police arrived only to be turned away by the ward staff, and the following morning Kane died of dehydration. The terrible misunderstanding was that the clinicians in charge thought Kane had diabetes mellitus. In fact, he had diabetes insipidus which, as this readership knows, is a totally different condition.

Rather than the getting fluids and desmopressin he desperately needed, he was getting his blood sugar monitored. Rita Cronin, Kane's mum, speaks with clarity and dignity about this. We resolved as an endocrine community to sort it out.

CHANGING THE NAME OF A CONDITION

There are very few conditions where the fix is so easy: fluids and desmopressin. It is not so easy, however, to know how to fix complicated healthcare systems. We decided to take a 'land, sea and air approach' – from all angles. This has included education (of clinicians, patients and the public), making desmopressin a critical medicine, and succeeding in commissioning a National Confidential Enquiry into Patient Outcome and Death (NCEPOD) enquiry, amongst other things. One blindingly obvious approach was that we should remove the word diabetes from the condition.

There need to be good reasons for name change. There is precedent for this: the rheumatologists got rid of the word Wegner as he was a Nazi. In the case of diabetes insipidus, the reason for change is that the old term is not fit for purpose in modern times. The obesity epidemic has literally swamped any chance of the term diabetes meaning anything other than sugar diabetes; diabetes=mellitus, case closed.

WHAT SHOULD WE CHANGE TO?

This is more difficult. Like naming a child, everyone has their favourite, unconscious bias is at play, and nothing in life is perfect. The sole ambition was always to remove the word diabetes. Names suggested and discarded along the way have included 'pituitary insipidus' (etymologically incorrect and not all patients have pituitary disease), 'ADH deficiency' (abbreviates to ADHD) and 'vasopressin deficiency' (abbreviates to VD – even worse!).

We settled on AVP deficiency (cranial DI) and AVP resistance (nephrogenic DI). The advantage is that it indicates both pathology and treatment in the same breath. Importantly, it was popular with the key players around the globe. We have now had approval for name change from the endocrine societies of the UK, Europe, the USA, Australia, South America, Japan and South East Asia. This is quite an achievement, and we are very proud of it.

Importantly, this could not have been done without patient support groups around the world, who have been our cheerleaders. The Pituitary Foundation has been amazing.

HOW DO YOU OFFICIALLY CHANGE THE NAME OF A CONDITION?

As they say on 'Bake Off', it has been a journey. We have had to learn about the worlds of ICD-11 (International Classification of Diseases 11th Revision; https://icd.who.int) and SNOMED CT (Systematized Nomenclature of Medicine – Clinical Terms; **www.england.nhs.uk/digitaltechnology/digital-primary-care/snomed-ct**).

We struck it lucky by finding a helpful influential contact at SNOMED CT. He thinks our case is perfect for name change and is helping us to adopt the new names in 32 countries around the world. For the first few years, we will use AVP-D and AVP-R as synonyms for cranial and nephrogenic diabetes insipidus, whilst keeping the 'parent' name DI to allow online searches to catch up, and to enable clinicians to use their preferred term.

Over time, the anticipation is that the new names will be accepted and become standard parlance. Eventually, just as HONK (hyperglycaemic hyperosmolar non-ketotic coma) has become HHS (hyperosmolar hyperglycaemic state) (HONK always sounded silly to me) and bronzed diabetes became haemochromatosis, it is likely that the 'Artist Formerly Known as Diabetes Insipidus' will graciously give way to its successors.

WHAT NOW?

We published an article in the August issue of *Lancet Diabetes & Endocrinology*, reporting an investigation of the perspectives of over 1,000 patients with DI (or whatever it's now called). Over 85% wanted name change.[2] Our publication in October of a position statement in the world's major endocrine journals should raise the profile of this initiative for endocrinologists.[1]

The main work is now for us all to shout this from the rooftops. We need your help to do this. We need to educate our fellow doctors, nurses, scientists, patients and the public. We aim to issue press releases in 2023 so that this is covered on TV, radio and social media.

We need to correct the damage done to Kane and his family, and the many others who have come to harm. After all, Kane's mum Rita has promised me that she'll be alongside us on the breakfast TV sofa!

MILES LEVY
Consultant Endocrinologist
Member of the Working Group for Renaming Diabetes insipidus

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Although the condition might be rare...

...the features are common

Perhaps it's Cushing's syndrome, perhaps it's something else? If you connect any of these dots within a patient, consider referring them to a specialist endocrinologist.

For a clinician's guide to recognising Cushing's syndrome's signs and features, email **cushings@connectthedots.health** and help shine a light on this rare condition.

HRA Pharma Rare Diseases

Connect the dots

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