Stress: from mitochondria to man

Time for a new name?
DIABETES INSIPIDUS
P22

Welcoming two new officers
ELEANOR DAVIES & DUNCAN BASSETT
P24–25

NEW LOOK SCIENCE
Improved websites for Society journals
P23

THYROID DRUG SURVEY
Endocrine Network takes action
P26

IN THE CLASSROOM
Nurse becomes teacher
P28

www.endocrinology.org/endocrinologist
The World Health Organization describes stress as the ‘health epidemic of the 21st century’, but our understanding of it begins with the work of Hans Selye, the Hungarian–Canadian endocrinologist.

Later known as ‘the father of stress’, his early research involved injecting mice with extracts of various organs and observing atrophy of the lymphoid tissue, adrenal enlargement and peptic ulcers. He initially thought he had discovered a new hormone, but later realised that this was the uniform response to every irritating substance he injected. He subsequently coined the term ‘stress’. In a note to Nature in 1936, Selye described three stages of alarm, resistance and exhaustion: responses that are well known to those grappling with winter pressure demands or research and education deadlines!

The feature articles in this issue of The Endocrinologist delve into various aspects of stress, from mitochondria (described in Gabriele Saretzki’s piece on oxidative stress on page 11) to man (as Adnan Agha relates in his account of burnout in healthcare professionals on page 8).

In his transatlantic article (page 6), Bruce McEwen focuses on the biological impact of experiences on mitochondrial function (described in Gabriele Saretzki’s piece on oxidative stress on page 11) to man (as Adnan Agha relates in his account of burnout in healthcare professionals on page 8).

The importance of circadian clocks for stress, sleep and well-being with David Ray (page 9). On page 12, Chris John describes how he has used stress as a learning and teaching platform! Sirazum Choudhury, Tricia Tan and Bernard Khoo argue for the need to redefine the cortisol stress response on page 14.

We explore the importance of circadian clocks for stress, sleep and well-being with David Ray (page 9). On page 12, Chris John describes how he has used stress as a learning and teaching platform! Sirazum Choudhury, Tricia Tan and Bernard Khoo argue for the need to redefine the cortisol stress response on page 14.

Katherine White highlights emotional stress as a trigger factor for adrenal crisis (page 16). On page 19, we gain an insight into how glucocorticoids can restore balance during stress, in an article by Giorgio Caratti, Pauline Pfänder and Laura Matthews. Finally, Mark Gurnell has written a brilliant piece (page 20) on stress in the world of finance, and endocrine influences on financial markets.

I do hope that perusing the winter issue of The Endocrinologist will help alleviate some of the stress associated with this time of year!

With warmest wishes and season’s greetings

AMIR SAM

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


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.
SUCCESS FOR SfE BES 2018

Thanks to everyone who contributed to the success of the recent Society for Endocrinology BES conference in Glasgow. More will follow in the next issue of The Endocrinologist.

OPPORTUNITIES TO JOIN THE ENDOCRINOLOGIST

We currently have vacancies on the Editorial Board at The Endocrinologist, to be filled in early 2019. If you are a Society member and would like to help showcase the latest thinking in all areas of endocrinology, please apply by emailing media@endocrinology.org for further details.

ENCOURAGING COLLABORATION

Your Society is sponsoring a symposium focusing on the relationship between stress and the endocrine system at the British Neuroscience Association’s Festival of Neuroscience in Dublin, Ireland, on 14–17 April 2019. Society for Endocrinology members can enjoy reduced registration fees for this partner society event.

MEDAL OF HONOUR

Congratulations to Charis Eng, Chair of Cleveland Clinic’s Genomic Medicine Institute and Editor-in-Chief of Endocrine-Related Cancer, who has been awarded the prestigious American Cancer Society’s Medal of Honor.

SOCIETY ENDorses OBESITY POSITION STATEMENT

The Society concurs with leading experts and has endorsed a new position statement that supports the recognition of obesity as a disease. Read this and other Society position statements at www.endocrinology.org/clinical-practice/society-position-statements.

WITH THANKS

Karen Chapman and Simon Pearce finished their terms of office as Society General Secretary and Programme Secretary, respectively, in November. Our grateful thanks go to both of them for all their hard work and input during their tenure. You can read interviews with their successors on pages 24–25.

HELP IMPROVE MEDIA REPORTING

Become a Society Media Ambassador and share your expertise to help improve science and health reporting in the media. Media Ambassadors work alongside the Society’s Press Office to provide accurate and responsible media reporting of endocrinology-related topics. Find out more in our free guide at www.endocrinology.org/outreach/public-engagement/opportunities/engaging-with-the-media.

WITH REGRET

We are very sorry to announce the death of Professor Vivian HT James, formerly of St Mary’s Hospital, London. Professor James served as Treasurer of the Society for Endocrinology and Editor of Endocrine-Related Cancer. An obituary will follow.

We wish all our readers a very merry Christmas and happy new year

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SOCIETY CALENDAR

12 March 2019
NATIONAL CLINICAL CASES 2019
London, UK
8–10 April 2019
ENDOCRINE ACADEMY: CLINICAL UPDATE 2019
Birmingham, UK
8–9 April 2019
ENDOCRINE ACADEMY: ENDOCRINE NURSE UPDATE 2019
Birmingham, UK
11–13 November 2019
SfE BES 2019
Brighton, UK

SOCIETY SUPPORTED EVENTS

14 February 2019
OBESITY UPDATE 2019
London, UK
14–17 April 2019
BNA 2019 FESTIVAL OF NEUROSCIENCE
Dublin, Ireland
25–30 August 2019
SPETSES SUMMER SCHOOL – NUCLEAR RECEPTORS, EPIGENOMICS, AND DISEASE
Spetses, Greece

GRANT AND PRIZE DEADLINES

13 March 2019
TRAVEL GRANT
13 March 2019
SUMMER STUDENTSHIP
27 March 2019
PUBLIC ENGAGEMENT GRANT
3 April 2019
REGIONAL CLINICAL CASES GRANT
10 April 2019
PRACTICAL SKILLS GRANT
8 July 2019
SOCIETY MEDAL NOMINATIONS
8 July 2019
ENDOCRINE NURSE AWARD NOMINATIONS

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

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

We can highlight your job opportunities to join the endocrine community.

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HOT TOPICS

SOCIETY FOR ENDOCRINOLGY OFFICIAL JOURNALS

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

JOURNAL OF ENDOCRINOLOGY

miR-132 improves β-cell function in mice

In recent years, microRNAs, a class of small, evolutionarily conserved, non-coding RNAs, have emerged as key regulators of processes in pancreatic islets, including β-cell function, proliferation and survival. Previous studies have found one of these, miR-132, to be highly expressed in the pancreatic islets of several obesity models, resulting in enhanced glucose-stimulated insulin secretion in vivo.

Mulder and colleagues therefore explored whether over-expression of miR-132 could have a potential therapeutic benefit in insulin-resistant conditions. They injected viral constructs containing miR-132 into the pancreatic duct, leading to its expression specifically in β-cells of pancreatic islets. They found that increasing miR-132 levels in β-cells improved glucose tolerance in mice fed a high-fat diet. Furthermore, in line with previous findings, islets isolated from these mice also secreted more insulin in response to glucose.

Their findings highlight the potential beneficial effects of modulating miRNAs to improve β-cell function.

Read the full article in Journal of Endocrinology doi:10.1530/JOE-18-0287

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Promoting anti-inflammatory macrophage responses in metabolic disease

Inflammation associated with obesity plays a key role in the pathogenesis of metabolic-related diseases such as metabolic syndrome and type 2 diabetes. Obesity-associated inflammation is characterized by failure of anti-inflammatory control mechanisms and predominance of a pro-inflammatory phenotype in peripheral blood mononuclear cells (PBMCs). Mesenchymal stem cells (MSCs) have immunomodulatory properties that may alter inflammation and affect the phenotype of PBMCs. However, the safety of therapeutic infusion of MSCs has limited their potential use.

Kruger et al. investigated anti-inflammatory effects of conditioned media from adipose tissue-derived MSCs (ADSC-CM) on phenotype and function of PBMCs from patients with and without metabolic syndrome. PBMCs were isolated from three groups of patients (healthy lean, overweight/obese with metabolic syndrome), and cultured with ADSC-CM. PBMCs from all patients were sensitive to ADSC-CM, which promoted an anti-inflammatory phenotype and secretion of anti-inflammatory cytokines such as interleukin 10. This effect was most pronounced in PBMCs from overweight/obese patients.

This study highlights the therapeutic potential of ADSC-CM to influence inflammation in obese patients. Further studies are needed to define the factors which promote the anti-inflammatory phenotype of PBMCs.

Read the full article in Journal of Molecular Endocrinology 61 173–184

ENDOCRINE-RELATED CANCER

Pseudohypoxia, ciliary loss and phaeochromocytoma

Cilia are important organelles for key signalling pathways, such as the Wnt and mammalian hedgehog pathways. Loss of primary cilia is observed in certain cancers.

O’Toole et al. have demonstrated that cilia are fewer in number and shorter in length in phaeochromocytoma tissue, compared with normal adrenal medulla. This was significantly associated with the presence of a germline VHL or SDHx mutation. Compared with normal adrenal medulla, phaeochromocytoma tissue was also found to have altered expression of genes associated with cilia-mediated signalling.

Using the rat phaeochromocytoma cell line PC12, the authors showed that pharmacological and genetic manipulation of succinate dehydrogenase (SDH), fumarate hydratase (FH) and hypoxia inducible factor (HIF) affect primary cilia (the VHL gene codes for a protein critical for HIF regulation). Data suggest that SDH and FH inhibition, producing excessive oncometabolites and thus pseudohypoxia, promoted ciliary loss. Hypoxic cell culture conditions produced a similar effect. Conversely, HIF inhibition protected against ciliary loss, as did inhibition of the cilia resorption pathway controlled by Aurora-A/HDAC8.

It appears that loss of cilia in phaeochromocytoma at least partly results from pseudohypoxic/hypoxic signalling.

Read the full article in Endocrine-Related Cancer 26 165–180

ENDOCRINE HIGHLIGHTS

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

Soy-based formula milk and menstrual pain

Development of reproductive system components involved in the pathophysiology of menstrual pain begins in utero and continues during infancy. Exogenous oestrogenic exposure in infancy (such as to soy-based formula) could plausibly result in persistent changes, leading to menstrual pain in adulthood.

Upson et al. gathered data from 1696 African-American women aged 23–35 years. Whether they were fed soy formula as babies, how long for and whether this started within 2 months of birth was noted by self-administered questionnaire for 1553 participants, 89% of whom were assisted by their mothers. Information on menstrual pain indicators was collected by web and telephone interview. Women ever fed soy formula as infants were more likely than unexposed women to report use of hormonal contraception for menstrual pain (RR 1.4, CE 1.1–1.9) and moderate/severe menstrual discomfort/pain with ‘most periods’, but not ‘every period’, in early adulthood (ages 18–22 when not using hormonal contraception) (RR 1.5, CE 1.1–2.0).

This adds to the growing literature on the reproductive health consequences of early life exposure to soy formula.

Read the full article in Human Reproduction doi:10.1093/humrep/dey303
Reliability of clonidine testing in diagnosis of GHD

Diagnosis of growth hormone deficiency (GHD) is currently based on clinical, auxological, biochemical and neuroradiological investigation. Provocative tests of GH secretion using physiological/pharmacological stimuli are required to confirm GHD, with the clonidine test (CT) widely used to assess GH secretory status. In a retrospective study, Ibba et al. analysed the reliability of the CT and the false-positive responses was 3.3%.

The results confirm that the CT is a reliable and safe GH-releasing test in both prepubertal and pubertal children. Read the full article in Clinical Endocrinology 89 765–770

Wound healing with honey

Although honey has been used as a wound dressing for hundreds of years, only recently has it attracted scientific interest because of its relevant antimicrobial, anti-inflammatory and anti-oxidant properties and nutritional content.

This case report by Teobaldi et al. is the first to highlight the use of honey dressings (glucose oxidase-positive with peroxide activity) in treatment of an ulcer with tendon exposure in a patient with type 2 diabetes. The use of the honey dressing, in addition to systemic antibiotic therapy, surgical toilette and skin graft, facilitated timely wound healing.

Further studies are required to validate this result. However, such treatment may constitute part of the comprehensive management of diabetic wounds, including those with tendon exposure, and should be considered in clinical practice. Honey dressings could be a low cost alternative to currently available, often expensive, dressings.

Read the full article in Endocrinology, Diabetes & Metabolism Case Reports EDM 180117

Hormones at high altitude

Humans cannot live at high altitudes because we cannot elicit long term physiological adaptation of the cardiorespiratory, metabolic and reproductive systems in such a hostile climate.

As hormones play a key role in regulating these processes, von Wolff et al. investigated whether the endocrine system becomes significantly dysregulated at a certain altitude. This observational cohort study assessed the impact of high altitude on 21 male and 19 female participants during an expedition in Nepal. The effects of altitude and hypoxia on stress, thyroid and hypothalamic-pituitary-gonadal hormone axes were assessed at baseline (550m) and at altitudes of 4844, 6022 and 7050m.

Hormone concentrations correlated with altitude but not with oxygen parameters, indicating that hypoxia was not a major driver of hormonal dysregulation in this context. Adrenal, thyroid and gonadal axes were affected by altitude, characterised by activation of the adrenal and thyroid axes and inhibition of the male reproductive endocrine axis. Aclimatisation at 4844m led to normalisation of adrenal and gonadal but not thyroid hormone axes. At higher altitudes (>5000m), endocrine dysregulation was pronounced, which may contribute to the incapability of humans to live permanently at very high altitude.

Read the full article in Endocrine Connections 7 1081–1089

Sex differences in action of ERα on insulin

Oestrogen has a positive impact on glucose homeostasis in both males and females, mainly through its actions on oestrogen receptor α (ERα). In cells, ERα is present both in the nucleus and at the level of the membrane, but the contributions of the different pools of ERα to glucose homeostasis were unknown.

Thus, Allard et al. studied both male and female mice expressing either the membrane or the nuclear pool of ERα to determine their contribution to glucose homeostasis, insulin action and insulin secretion. Findings suggest that nuclear ERα plays a dominant role in the metabolic actions of oestrogen.

Interestingly, the authors found sex differences in the mechanism of action; in females, nuclear ERα impacts on central insulin action and the modulation of hepatic glucose production. In contrast, in males, its actions are related to the central response to glucose as well as neural control of insulin secretion.

This study provides further support for the importance of developing sex-specific therapies in diabetes.

Read the full article in Diabetes doi:10.2337/db18-0993

Diet and the mammary gland microbiome

That a Mediterranean diet might protect against breast cancer has been suggested by several human studies. Now, Shively and co-workers provide evidence that the mammary gland microbiome might form part of the explanation.

Female macaque monkeys were fed either a Western diet or a Mediterranean diet for 31 months. The Western diet was low in fibre, high in sucrose and high in animal fats. The Mediterranean diet had a higher fibre content and lower sucrose, and olive oil was the chief source of dietary fat.

Mammary gland tissue was then analysed to characterise its microbiome and metabolome. Compared with a Western diet, monkeys fed a Mediterranean diet had a 10-fold higher prevalence of Lactobacillus. They had a lower abundance of Ruminococcus and Lachnospiraceae bacteria. Metabolomic analyses demonstrated a reduction in metabolites associated with oxidative stress and inflammation in the Mediterranean diet cohort. Some of these beneficial metabolites are those which have undergone bacterial processing (from tryptophan into indole products, for example).

The authors therefore suggest that the microbiome might contribute to the mechanism by which diet influences breast cancer risk.

Read the full article in Cell Reports 25 47–56
I have borrowed the title of this article from a book I wrote with Elizabeth Norton Lasley in 2002. ¹ The purpose of this article, like the book, is to redirect thinking away from the rather broad and ambiguous meaning of ‘stress’ as a concept and a word. Instead, the aim is to focus on the biological impact, both good and bad, of experiences throughout the life course, whether or not we call them ‘stressful’. Hormones play a key role in what happens, acting on both the brain and the rest of the body. ²

WHAT IS ‘STRESS’?
‘Stress’ is everywhere in our daily experiences and conversations and yet, except for describing the ‘fight or flight’ response, most people do not understand what is going on in the brain and body.

We become anxious when hearing about violence, chaos and discord. The pace of our daily lives, and the demands upon us and our children, often lead us to feel that there is too much to do in so little time! This disrupts our natural biological rhythms and encourages unhealthy behaviours, such as eating too much of the wrong things and neglecting exercise and good sleep. The result is in an unhealthy lifestyle.

Poverty and racial and ethnic discrimination, and a lack of educational opportunities and economic advancement, take their toll. Adverse experiences in infancy and childhood, including poverty, leave a life-long imprint on the brain and body. This undermines long term health, increasing the incidence of cardiovascular disease, diabetes, depression, substance abuse, anti-social behaviour and dementia.³

How does all of this stress ‘get under our skin’? What does it do to our brains and our bodies, how does it do it, and what can we do about it?

CATEGORISING STRESS
For starters, ‘good stress’ involves our taking a chance on something we want, such as interviewing for a job or school, or giving a talk before strangers, and feeling rewarded when we are successful. ‘Tolerable stress’ means that something bad happens, for instance failing to get that job or position in school, losing a job or experiencing the death of a loved one, but where one has the personal resources and support systems to weather the storm.

‘Toxic stress’ means that something bad is going on but in circumstances where one does not have the personal resources or support systems, resulting in a lack of control. As a result, over time, one may suffer mental and physical health problems, particularly if the situation is not resolved. This occurs through a gradual process called ‘allostatic load and overload’.

‘Homeostasis’ means the physiological state which the body maintains to keep us alive: that is body temperature and pH within a narrow range and an adequate oxygen supply. In order to maintain homeostasis, the body activates via ‘allostasis’ the release of mediators like cortisol, adrenaline, the immune system, the autonomic nervous system, metabolism and neurochemical systems in the brain to promote adaptation (Figure 1). This occurs, for example, when we get out of bed in the morning, walk up a flight of stairs, are surprised by something unexpected, get into an argument, or run to catch a train.

We may only refer to some of these experiences as ‘stressful’ and thus the word does not really recognise all of the underlying biology. The mediators help us adapt as long as they are turned on in an orchestrated and balanced manner and turned off efficiently when not needed. ‘Allostatic load’ is when this happens over weeks and months and produces, for example, an accumulation of abdominal fat or hypertension, i.e. an ‘allostatic state’. ‘Allostatic overload’ refers to what occurs in toxic stress and may lead to disease, e.g. coronary artery blockade or diabetes or depression.

WHAT ABOUT CORTISOL?
Because cortisol is well known in relation to stress, we often hear that measuring our cortisol levels will tell us if we are ‘stressed’. But this is not so simple.

First, a single measure of cortisol will tell us nothing, since cortisol levels go up and down within minutes. Rather, multiple samples over time, urinary cortisol collection or hair cortisol can be used to assess excess or insufficient cortisol secretion.

Secondly, cortisol helps us adapt, working along with the other mediators of allostatics. Cortisol co-ordinates metabolism with daily activity and sleep patterns.⁴ Diurnal fluctuations of cortisol promote the formation and elimination of synapses in the brain and this helps us learn and adapt.⁵ Furthermore, the diurnal early morning rise of cortisol, as well as a stress response, activates adaptive immune function and sends immune cells ‘to their battle stations’ to fight an infection or repair a wound.⁶ However, too much cortisol also causes problems, as do a flat diurnal rhythm and Cushings’s disease, when excess cortisol is stimulated by a pituitary gland tumour!

Thirdly, glucocorticoids do not play the same role across the life course, but rather serve different functions. This starts with their role in ‘wakening’ of the amygdala in neonatal life to their role in promoting ponderal growth in adolescence⁷ and their influence on the vulnerability of the adolescent brain to stressful experiences⁸,⁹ as well as the age-accelerating role of excess cortisol.¹⁰¹¹ Cortisol affects multiple functions via non-genomic and genomic mechanisms (Figure 2).

HEALTH-IMPACTING BEHAVIOURS
It is important to note that health-damaging behaviours are major contributors to allostatic load and overload. These are often the result of


Figure 1. The brain is the central organ that perceives and responds to events that are potential threats and directs both physiological and behavioural responses. Hormones play a key role and signal back to the brain to affect behaviour and brain architecture.
and became the ‘gateway’ for other discoveries regarding brain‒body experiences (Figure 3).

plastic and vulnerable organ of the body, and is continually sculpted by

show that, although ‘reversal’ is not possible, redirection of brain function

emerged and have revealed mechanisms of steroid hormone action other than direct genomic stimulation. These include actions on mitochondria as well as regulation of cellular signalling pathways.19,20

Besides steroid hormones, metabolic hormones enter and affect the brain and their relationship to brain metabolism, and mitochondrial function has become important for understanding disorders like diabetes, depression and dementia.21 Another important hormone discovery has been the widespread effect of sex hormones throughout the brain, along with diverse mechanisms for sex hormone action at both genomic and non-genomic levels, including actions in mitochondria.22,23 This has helped highlight the need to understand sex differences in normal brain function and disease and in relation to stress and allostatic load.

Finally, hormone actions via epigenetic mechanisms operating over the life course are changing the way we look at the development of disorders and the possibilities for intervention.24,25

WHAT DOES THIS MEAN FOR INTERVENTIONS?

Discovery of hormone receptors and actions throughout the brain2 has led to the discovery of its capacity for allostatic adaptive structural and functional plasticity, mediated in part by hormones. This has helped to facilitate the emergence of practical aspects of the science of ‘epigenetics’ by revealing effects of the social and physical environment on adult as well as developing brain structure and function. Gene expression studies show that, although ‘reversal’ is not possible, redirection of brain function and behaviour is possible via the capacity for plasticity as the life course unfolds.26

Early life adversity, along with preconception and prenatal events, has disproportionately strong and lasting effects on cognitive, mental and physical health. While prevention is key, the epigenetic view shows that there are on-going possibilities for amelioration via behavioural interventions. These involve increased physical activity, social support, mindfulness and meditation, and are being shown to change brain structure and function as well as to benefit systemic physiology.27–29

BRUCE S McEwen
Alfred E Mirsky Professor, Head, Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, Rockefeller University, New York, NY, USA

REFERENCES
1. McEwen BS & Lasley EN 2002 The End of Stress As We Know It. Washington, DC, USA: Joseph Henry Press.

Figure 2. Glucocorticoids (GC) have multiple roles and mechanisms of action besides direct and indirect genomic regulation. These include mediating direct release of the neurotransmitter glutamate, activation of endocannabinoid (eCB) secretion that feeds back on presynaptic glutamate and GABA (γ-aminobutyric acid) release, and actions on mitochondria. CB1 receptor, cannabinoid 1 receptor; CREB, cAMP response element-binding protein; GR, glucocorticoid receptor; mG, membrane-bound GR; MR mineralocorticoid receptor. ©BS McEwen

Figure 3. Hormones are involved in regulating brain architecture that includes remodelling of dendrites, turnover of synapses and neurogenesis in the adult as well as in the developing brain. ©E Gould, Princeton University

CENTRAL ROLE OF THE BRAIN

The brain ‘keeps the score’ by storing memories from bad as well as good experiences and promotes the ‘wisdom of the body’ by choices it makes, such as adopting health-promoting behaviours.18 Indeed, the brain is a plastic and vulnerable organ of the body, and is continually sculpted by experiences (Figure 3).

Discovery of adrenal steroid receptors in the hippocampus led the way and became the ‘gateway’ for other discoveries regarding brain–body interactions.2 Cellular and molecular mechanisms for this plasticity have emerged and have revealed mechanisms of steroid hormone action other than direct genomic stimulation. These include actions on mitochondria as well as regulation of cellular signalling pathways.19,20

health-damaging behaviours imposed by life stressors, e.g. not only poor diet, smoking or alcohol but also poor sleep, loneliness and lack of exercise (Figure 1). And they do so through the same mediators of allostatics.4,15

Family conflict, neighbourhood chaos, the demands of a job, shift work and jet lag or living in an ugly, noisy and polluted environment all contribute to allostatic load/overload through the same biological ‘mediators’ that promote adaptation – and they shape our brains as well!
Simply put, ‘burnout’ is defined in the words used by renowned psychologist Christina Maslach, nearly four decades ago: ‘What started out as important, meaningful and challenging work becomes unpleasant, unfulfilling and meaningless. Energy turns into exhaustion, involvement turns into cynicism and efficacy turns into ineffectiveness.’ Does that ring a bell for any of my NHS colleagues?

The term ‘burnout’ is often used synonymously with stress/work-related stress, but it is a separate health condition coded in the ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th Revision), resulting from continuous and long term stress exposure, particularly related to psychosocial factors, and chronic emotional and interpersonal job stressors.

Stress and burnout are essentially different, as stress is characterised by over-engagement, hyperactivity and loss of energy and can lead to anxiety disorders, while burnout is characterised by disengagement, a feeling of helplessness/hopelessness and loss of motivation and can lead to depression and depression.

Burnout is identified by the presence of one or more of three features:
- emotional exhaustion: a depletion of sentiments/feelings
- depersonalisation: such as being detached/callous towards patients (e.g. rather than ‘Mrs Smith developed diabetic ketoacidosis (DKA) due to insulin availability’, saying ‘Bed 9 is DKA due to non-compliance’)
- lack of personal accomplishment: a reduced sense of achievement/satisfaction from work.

As burnout is fundamentally a work-related condition, the only guaranteed way to have no burnout would be to not work at all.

What started out as important, meaningful and challenging work becomes unpleasant, unfulfilling and meaningless. Energy turns into exhaustion, involvement turns into cynicism and efficacy turns into ineffectiveness.’

BACKGROUND
The ‘history’ of burnout began in 1974, when Herbert Freudenberger first coined the term. A few years later, Christina Maslach not only defined burnout and its dimensions, but also came up with a tool to measure it (the Maslach Burnout Inventory) which is still the most widely used questionnaire globally. The other tools used to assess burnout include the Oldenburg Inventory and the Copenhagen Survey, but none of them are able to assess all three dimensions of burnout.

CAUSES AND EFFECTS
The mechanism by which burnout occurs is complex, but it generally arises from a lack of resources, demands of work overload, personal conflicts and a lack of coping mechanisms. Burnout develops over a period of time, usually a few months.

Burnout syndrome is considered to be a predictor for developing depression, absenteeism, decreased capacity to cope with stress and a decline in working ability, alongside an increased risk of eating disorders, overweight, obesity, coronary heart disease and myocardial infarction. Healthcare professionals with burnout also find it more difficult to motivate patients who need constant engagement and have longer term conditions.

PREVALENCE
At present, UK workforce data do not identify burnout in particular, or differentiate it from stress. However, if we look at data from 2016, they show that work-related stress (including burnout) accounted for 37% of all work-related cases of ill-health and 45% of all working days lost due to ill-health. Thus it was the highest reported work-related illness, with an average of 25.9 working days lost per worker.

Burnout seems to affect healthcare professionals nearly twice as much as an average member of the working population. This is probably because we are trained to put the needs of others before ourselves, and spend each working day exposed to the emotional/physical strain of dealing with people who are sick or dying.

IMPACT ON THE NHS
Regarding the NHS, the annual cost of sickness absence in its staff due to burnout is £2.4 billion (2.3% of the NHS budget). Various studies using the Maslach Burnout Inventory have shown that the prevalence of burnout among UK doctors may be as high as 40%. Similarly, a study in nursing staff across ten European countries shows that 42% of UK nurses report burnout compared with a European average of 28%. The results from a recent national survey of diabetes specialist registrars show that 58.5% of them have burnout.

SUPPORT
The bright side is that more than 25% of workers affected with burnout can improve by means of stress management, using interventions such as mental and physical relaxation, flexibility in work schedules and resiliency training. The best results are seen with organisational interventions that focus on a reduction in specific stressors.

It is important for us to be able to screen, identify and manage burnout in healthcare professionals. Countries such as Belgium introduced legislation making it mandatory for large organisations to assess burnout in their employees annually, and we probably need to follow suit.

I feel that it is important for us to be able to screen and identify burnout in our healthcare professionals at least at a Trust level. Tailor-made institution-based interventions can then be applied to manage the condition. But we need to take the first step…

ADNAN AGHA
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All life on Earth is subject to predictable changes in the environment, as the rotation of the planet results in alternating day and night. There is a major survival advantage in anticipating these changes, rather than reacting to them, and this has supported the acquisition of circadian timing mechanisms in all kingdoms of life. Although the design principles remain constant, the genes involved vary, suggesting discrete evolutionary development.

A constant feature of all circadian timing systems is a positive arm. This activates transcription of genes, which result in the synthesis of proteins, which then act to repress the positive arm. The serial time delays involved in transcription, translation, modification of proteins and subsequent achievement of critical concentrations to repress the active arm gives the period of the oscillation: approximately 24 hours.

The core cellular circadian mechanism is relatively resistant to the external environment, but does retain a resetting response to changes in external cues such as light or feeding. It is this resistance to change that we perceive as jet lag.

**A CENTRAL CLOCK**

In mammals, the development of a solid cranial prevented detection of sunlight by deep brain photoreceptors. Therefore, light sensing for circadian entrainment takes place through the retina, with a specific neural projection to the central brain clock, the suprachiasmatic nucleus (SCN).

Interestingly, light entrainment of the central clock can be dissociated from image formation in the primary visual cortex. A major photoreceptor in the retina, melanopsin, which is expressed on a subset ofretinal ganglion cells, has evolved to detect short wavelength, blue, light, and to transmit this daylight signal to the SCN.

In addition to the central brain clock in the SCN, it has emerged that virtually all cells have their own circadian machinery, and are capable of sustained circadian oscillations, even when cultured *ex vivo*. Therefore, the SCN serves as a synchronising centre, ensuring that the diverse clocks through the body ‘tick in time’. It is thought that neural and humoral signals act on peripheral cells to correct drift in timing, rather like the actions of the Greenwich time signal used to set clocks and watches in our homes.

Amongst the most important humoral signals are glucocorticoids (GCs). Indeed, in early studies, cultured cells were synchronised by application of a short pulse of high dose GC.

**THE CLOCK AND GLUCOCORTICOIDS**

Discovery that the clock was regulated by the stress hormone GC was followed by further work showing that the GC receptor was itself regulated by the clock. Both the availability of ligand, cortisol, and also the function of the GC receptor, were found to vary across time, with profound effects on organ function.

We, and others, have characterised major impacts on inflammation, and its GC regulation, and also energy metabolism, and its regulation by GC. Therefore, the long recognised circadian variation in serum cortisol that we all recognise is only part of the picture. There is also a marked variation of GC sensitivity across the circadian period.

**ENERGY METABOLISM**

The role of the clock is very strong in energy metabolism. The move from activity and feeding during the day to rest and fasting by night requires a major rewiring of hepatic, adipose and muscle energy metabolism.

More than 90% of the liver genes involved in lipid synthesis lie under strong circadian control. Consequently, the impact of feeding at different times of the day has attracted attention. Striking studies in mice suggest that restricting feeding times is an effective means to prohibit development of obesity, even in the presence of a high fat diet and excess calorie intake. Furthermore, even people on standard activity and feeding schedules show a marked change in insulin sensitivity across the circadian day, with implications for clinical trials, biomarkers and, in time, clinical management.

**SLEEP DISORDER**

Sleep and its disorders are highly prevalent, and the most frequently reported co-morbidity in long term disease. Most doctors feel under-equipped to manage sleep disorders, and there is a lack of effective pharmacological options. Psychological approaches can be effective, but are slow, expensive and not widely available.

The major drives to sleep are a homeostatic drive, which increases from the time of waking, and a circadian input. These two inputs explain the drowsiness that arrives in the afternoon, and the difficulties in sleeping well when jet-lagged.

Sleep deprivation is common in modern societies, with implications for mental and physical health. Sleep deprivation and sleep disruption, such as in shift-working, result in changes in energy metabolism, and in changes in behaviour. There is evidence for altered food selection in tired people, which may explain the excess risks of obesity and type II diabetes in long term shift-workers. Acute sleep deprivation exerts a profound effect on the serum metabolome and proteome, and affects the adaptive immune system, as determined by variation in vaccination efficacy. Human sleep studies are now benefitting from advances in genetics, brain imaging and experimental medicine, and have widespread implications for social policy and medicine.

Chronotype refers to the timing preference of a person. Early chronotypes favour mornings, and late chronotypes the evenings – or ‘larks’ vs ‘owls’. Recent large scale genetic studies have identified a number of genes affecting human chronotype, supporting the existence of hard-wired traits. In addition, rare individuals have marked changes in chronotype, manifest by persisting and intractable sleep phase disorder, due to mutations in core circadian clock genes.

There are also changes in chronotype with age and gender. In particular, the teenage years are characterised by a marked late chronotype, with boys more affected than girls. The can affect school attendance and academic achievement, leading some schools to alter start times. It is unclear why adolescents would gain from having a distinctly delayed period of preferred activity compared with their parents and younger siblings.

**A CHALLENGE FOR ENDOCRINOLOGISTS**

Taken together, circadian mechanisms underpin many of the systems that we, as endocrinologists, study and treat. There remains much to understand, and the challenges of translating the fascinating scientific advances in the field to the clinic remain. However, the time for the circadian clock is now, as recognised by the award of last year’s Nobel Prize, and the challenge is laid down for us to accept.

**DAVID RAY**

Professor of Endocrinology, University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford
The ageing process is complex and its detailed mechanisms are not yet well understood. However, cellular senescence might play an important role.

WHAT IS SENESCENCE?
Cellular senescence in its various forms – replicative, premature or oncogene-induced – is a stress response.1 Senescence is an irreversible growth arrest. However, post-mitotic cells can also become senescent, although without the growth arrest feature.2

Replicative senescence is best characterised in human somatic cells such as fibroblasts by a continuous telomere shortening.3 However, telomere shortening can be accelerated by increased oxidative stress4,5 and thus has immediate significance for the ageing process, where telomeres are thought to be a possible biomarker.6 However, this is often just related to average telomere length while there is large heterogeneity between individual telomeres,7 a dynamic regulation of telomere homeostasis by telomerase and TERRA telomere transcription products8,9 and, most importantly, there can be DNA damage in telomeres without shortening.10,11

The direct association between senescence and the ageing process has been demonstrated by ablating these cells from an organism, either genetically12 or by using senolytics.13 Lopez-Otín et al. have provided a comprehensive characterisation of the ageing phenotype.14

THE ROLE OF MITOCHONDRIA
Most oxidative stress within cells is generated by mitochondria. Mitochondrial dysfunction and increased reactive oxygen species (ROS) are features of senescent cells which can be ameliorated with uncouplers and ROS-scavenging agents.15 Paradoxically, mitochondria seem to be essential and required for senescence induction, while ablating them prevents senescence and associated features such as DNA damage and senescence-associated secretory phenotype (SASP).16

During senescence and ageing, there is an accumulation of pathological mitochondrial mutations while the mutation numbers do not increase.17 Importantly, there is a certain threshold of around 70–80% of mutated mitochondrial DNA molecules before a phenotype appears.

ROS are thought to be an important source of mitochondrial ROS. ROS are generated at different sites in the electron transport chain, in particular at complexes 1 and 3 during normal physiological functioning of mitochondria.18 There is also a reverse electron flow back from complex 2 to complex 1.19 Paradoxically, in some lower organisms, such as worms, flies, and yeast, it has even been shown that lowering mitochondrial ROS results in a decrease in organisal lifespan.20,21 It is known that ROS also have important signalling functions,22 so that complete scavenging of ROS has a rather detrimental effect for mitochondria, cells and organisms.

Recent discoveries show the presence and function of mitochondrial micro RNAs regulating mitochondrial oxidative phosphorylation,23 and of hormone-like mitopeptides, such as humanin, which are involved in regulation of cellular energetics, insulin sensitivity and glucose homeostasis.24

THE RELATIONSHIP WITH AGEING
An important research topic is the relationship between oxidative stress, mitochondria and ageing. It has long been known that ageing is associated with a low level, chronic inflammatory process25 and low level inflammation seems to correlate best with longevity in humans.26 Inflammation is also a prominent feature of many age-related diseases.27

To some extent, SASP which results in a lot of secreted pro-inflammatory molecules,28 might contribute to the process of inflammation and so-called “inflammaging”.29 Via dysfunction and ROS production, mitochondria directly contribute to SASP and senescence.30

Baker et al. have demonstrated in a senescence clearance mouse model that not only were life- and health-span increased, but also that expression of inflammatory genes was decreased upon removal of senescent cells in various tissues, including heart, muscle and kidney.31

While the master inflammation regulators NFκB (nuclear factor-κB) and IL-1α (interleukin-1α) were thought to be responsible for SASP,32 a new concept regarding a specific mitochondria-driven SASP has been presented (mitochondrial dysfunction-associated senescence or MiDAS).33 This, however, remains controversial amongst researchers working on ageing.

‘Dysfunctional mitochondria activate inflammation as well as senescence, and can stimulate the innate immune response. Thus, their role and that of cellular oxidative stress remains an important field of research.’

Nutrients and glucose stimulate signalling processes in senescent cells, such as the mTor and the NFκB pathways.34,35 NFκB has been shown to modulate oxidative phosphorylation via p53.36 Consequently, a lack of mitochondria reduced the inflammatory signalling in a cell model.37

Another type of inflammation can be induced during cellular injury and leakage of mitochondrial DNA and other components, such as cardiolipin, out of mitochondria. This process can activate damage-associated molecular patterns via pattern recognition receptors.38 Activation of toll-like receptors (TLR9)39 and cytosolic DNA sensors such as cyclic GMP-AMP synthase (cGAS)40 by mitochondrial DNA may be a result of the evolutionary origin of mitochondria and their resulting similarity to bacteria. In addition, ROS resulting from mitochondrial

continued on page 12…
dysfunction can activate the inflammasome\textsuperscript{17} while inflammation, in
turn, is able to induce senescence in neighbouring cells due to the so-called
`bystander effect'.\textsuperscript{18,39}

**IN CONCLUSION**

In summary, it is fair to state that mitochondria play an important
role in the induction of senescence as well as in ageing. New mechanisms
are constantly added regarding the detrimental role of excess ROS
generated during ageing and senescence. Dysfunctional mitochondria
activate inflammation as well as senescence, and can stimulate the innate
immune response. Thus, their role and that of cellular oxidative
stress remains an important field of research, while the prevention
of senescence using senolytics and senostatics has already reached a
translational state.\textsuperscript{30}

**REFERENCES**


**STRESS: AN EDUCATIONAL PANACEA?**

**WRITTEN BY CHRIS JOHN**

`Stress' was most definitely the hook that drew me into world of endocrinology in the first place. The year was 1996, and I had just completed my BSc in Pharmacology at King’s College London. I had decided to embark on a PhD, primarily to avoid facing the real world and getting a proper job.

I spent a summer looking for PhD opportunities in London, but was becoming disheartened due to the sheer number of projects which focused on obscure proteins acting in tissues of which I had never heard. Then, as the summer was drawing to a close, a beacon was lit in the shape of a project offered by Julia Buckingham at Charring Cross and Westminster Medical School. It had the simple title ‘Stress-induced infertility’.

The project appealed to me for two reasons. First, it appeared to be a project that involved whole body physiology and, secondly, I felt I had a clear understanding of the term ‘stress’. Having secured the PhD, I then spent the next 3 years working on the action of some obscure protein in a tissue of which I’d never heard. This was my first lesson in the art of marketing.

**STUDENTS AND STRESS**

However, my initial engagement with the concept of stress is certainly mirrored in the students who entered university in 2018. If you enter the terms ‘stress’ and ‘secondary education’ into a Google search, you will receive over 100 million results. The majority of these focus on exam stress and its impact on performance and mental health. Anyone involved in education at all will know that students are obsessed with performance in assessments above anything else. As a result, students are incredibly interested in the subject of stress before they even enter university.
Prior knowledge is an essential component of the learning process, so we have a student body that should be very receptive to any teaching concerning stress. That prior knowledge can be clearly demonstrated if you ask early years students to define stress (see Figure).

AN EXPERT’S DEFINITION
How would an expert define stress? From a teaching perspective, I’ve always liked an adaptation of Hooke’s Law (1658):

‘The magnitude of an external force, or stress, produces a proportional amount of deformation, or strain, in a material or an organism.’

As you can see from the Figure, even amongst ‘raw’ university students you will find definitions that are fairly accurate (and others less so).

TEACHING STRESS
So, how much do we teach our students about stress? I entered the term ‘stress’ into the search engine of our lecture capture software for the 2017–2018 academic year and received 757 hits! Those are 757 individual lectures across the course that relate to stress in some way.

Much of that teaching develops a deep understanding of the endocrinology of stress. Some examples include the link between stress and disease, such as the importance of the mineralocorticoid and glucocorticoid receptor balance in the hippocampus and how this determines the supportive or destructive role of cortisol in this tissue, which is linked to the potential development of depression.

Or there’s the difference in the typical male and female behavioural responses to stress, whereby cortisol is known to activate the amygdala (fear centre) and promote ‘flight’. The ‘flight’ response can be diminished by testosterone which switches the behavioural stress response towards a more aggressive ‘fight’ response, but can also be modified by oxytocin to induce a more ‘affiliative’ response (the ‘tend and befriend’ model).

There are many other examples that demonstrate how the endocrinology of stress is taught throughout our syllabus.

RESEARCHING STRESS
This year we introduced a 3-week research experience for our second year medics. This felt like a great opportunity to come full circle: creative ownership of a project focused on stress is what had driven my interest and passion for this subject over two decades ago. Once again stress was the perfect educational tool…

The project title was ‘Stress has a negative impact on exam performance’, which has personal relevance for all students (I’d learnt my marketing lesson many years before). In addition, non-invasive biomarkers for stress exist, meaning students could test this hypothesis with limited resources.

Ten groups of three students were given the task to design and test their own stress protocols. The creative element of the project engaged students in a manner I had not previously witnessed in all my years of teaching. A testing phase allowed students to modify stress protocols that included cold pressor stress, mild electric shock stress and a wide range of social stressors including the most powerful stressor tested — public singing!

LESSONS LEARNT
The experimental phase produced an interesting set of results. When asked how the project had changed their attitude to endocrinology, I received many student comments similar to the following.

‘In my efforts (research) to make sense of the results generated by this investigation, I came across numerous intriguing mechanisms that play a part in the stress response. A particularly fascinating example is the prospect that one’s personal disposition may contribute to whether or not hypothalamic-pituitary-adrenal axis activation occurs. This research experience has taken me past superficial assumptions about the endocrine system and has offered me a glimpse of the true depth and wonders of endocrinology.’

I felt extremely proud that our students had entered university with some understanding of stress, which we had substantially developed with extensive teaching on the subject. Finally, a deep understanding of the endocrinology of stress had been promoted, through creative engagement with stress in an experimental setting. A true educational panacea!

However, it appears that no panacea is absolute, as evidenced by the following response.

‘It hasn’t. The only relevance was coming up with a physiological explanation for the stress response. Other than that endocrinology was fairly obsolete. (Sorry?)’

For now, I’ll file that one under ‘how to stress an endocrinologist’.

CHRIS JOHN
Reader in Pharmacology, Head of BSc Biomedical Science, Director BSc Pharmacology, Section of Investigative Medicine, Hammersmith Campus, Imperial College London
The concept of stress derives from the pioneering work of Hans Selye. He took the term from physics to refer to a ‘non-specific response of the body to any demand’, where the body adapts initially to any condition which threatens to perturb homeostasis (‘the stressor’) via a co-ordinated and stereotyped response. This response depends on the acute release of neurotransmitters from the autonomic nervous systems as well as hormones from the adrenal cortex, adrenal medulla, pituitary and other endocrine glands.

AN INITIAL UNDERSTANDING
A central part of this stress response is the secretion of cortisol, mediated by corticotrophin-releasing hormone/arginine vasopressin and adrenocorticotropic (ACTH). From an endocrinologist’s point of view, patients with hypoaldrenism are unable to mount the stress response and are in danger of death from adrenal crises. Therefore, an understanding of the cortisol stress response is crucial to informing our treatment of hypoaldrenic patients, based on the time-honoured principle of prescribing additional steroid replacement in patients who are undergoing situations of physiological stress, such as illness or surgery, to mimic the physiological levels observed in these situations.

The classical understanding of the cortisol stress response comes from the seminal work of Plumpton and Besser in 1969. Twenty euadrenal patients were recruited to undergo an insulin tolerance test (ITT), prior to elective surgery that would now retrospectively be considered as at least major surgery, under the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) criteria.

All 20 had plasma cortisol levels measured at fixed intervals during their ITT and subsequent surgery. As their surgery was uncomplicated, with cortisol levels responding appropriately to surgical stress, their ITT results formed the reference against which ITTs have been interpreted over the last nearly 50 years (peak cortisol >580nmol/l, with a maximal increment of nearly 50 years (peak cortisol >580nmol/l, with a maximal increment of 1.4-fold from baseline).

Through the years, these cut-offs have been adjusted down to reflect the differences in assay used, with guidelines now recommending 500nmol/l as a cut-off.

Using surgical models as employed by Plumpton and Besser permits the simplest and most reproducible approach to understanding the clinical importance of the stress response.

A MODERN META-ANALYSIS
The cortisol response to surgery was assessed in a recent meta-analysis of 71 studies between 1990 and 2016 by Prete et al. Their survey shows that the severity of surgery does influence the cortisol stress response, where minimally invasive procedures produce no peri-operative cortisol peak and increasingly invasive procedures cause correspondingly larger cortisol peaks.

Following major surgery, cortisol levels are elevated for up to 7 days, although this is based on more limited data. Open surgery and the use of general anaesthesia also increase the cortisol response. They found that older patients and female patients had higher cortisol responses.

However, the conclusions that can be drawn from these meta-analytic results are limited by the highly heterogeneous nature of the studies included, in terms of patient selection, peri- and post-operative care, anaesthesia and relatively few patients undergoing minimally invasive surgery. Importantly, the long time base of the meta-analysis means that the results are influenced by considerable advances in anaesthetic techniques, surgical approaches and quantification of cortisol through the last three decades.

To consider the last point in more detail, cortisol assays have graduated from being highly non-specific assays exhibiting large positive biases (for example the fluorometric assay used by Plumpton and Besser) to become increasingly more specific immunoassays which now align reasonably well to reference methods such as gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry.

Ideally, mass spectrometry would be used to ensure high specificity for cortisol and to reduce interference from related molecules such as 11-deoxycortisol, but this technique is not widespread and immunoassays on analyser platforms remain the mainstay in most clinical chemistry laboratories, due to their low cost and speed of analysis.

Another shortcoming of most studies on the surgical stress response is that the response of cortisol-binding globulin (CBG) is not studied. Some 80% of the total serum cortisol that is measured is bound to CBG (10% to albumin), and CBG is a key regulator of free (and hence bioavailable) cortisol levels. Levels of CBG fall during physiological stress, including (crucially) surgery, leading to elevations in free cortisol. This suggests that even if total cortisol is unchanged, a reduction in CBG may lead to an increase in bioavailable cortisol.

‘A true appreciation of the cortisol stress response to surgery will require a study which utilises validated methods for directly measuring free cortisol, for example equilibrium dialysis.’

AN UP-TO-DATE STUDY
Taking these factors into account, we carried out a study where we examined 93 euadrenal patients undergoing elective surgery in a single centre. We deliberately recruited patients with a wide range of surgical interventions, classified according to the POSSUM scale. Examples of procedures were as follows.

• ‘Minor’ procedures included parathyroidectomy and diagnostic laparoscopy
• ‘Moderate’ procedures included laparoscopic appendicectomy and cholecystectomy, open thyroidectomy and open hernia repair
• ‘Major’/‘Major’ procedures included cardiothoracic procedures, such as coronary artery bypass grafts as well as open major abdominal surgery.

We studied the cortisol response using a modern immunoassay aligned to reference methods (Abbott Architect), as well as measuring the CBG response to surgery in 83 patients. The magnitude of the cortisol stress response correlated positively with surgical severity, although the cortisol
levels for ‘Minor’ procedures tended to fluctuate about patients’ respective morning baseline values, suggesting that, for these procedures, there is no marked cortisol stress response in most patients. We also found that total cortisol levels, even with ‘Major’ or ‘Major+’ surgery, often fell to baseline levels by post-operative day 1.

‘Despite nearly 50 years of study, the cortisol stress response continues to be poorly understood in many ways. Further research is essential to develop the evidence base for the proper treatment of our hypoadrenal patients.’

KEY FINDINGS
Our first take-home message is that a stratified approach to peri-operative adrenal replacement, as recommended by the Endocrine Society, may be a good approach to obviate adverse effects from over-treatment, especially in patients undergoing ‘Minor’ procedures. Based on the known pharmacokinetics of hydrocortisone, we believe that smaller induction doses of 25mg intramuscularly or orally for ‘Minor’/‘Moderate’ surgery and 50mg intramuscularly for ‘Major’/‘Major+’ surgery should be able to cater for any cortisol requirements with a safety margin.

Our second take-home message is based on our observation that CBG levels fall with surgery by up to 40% or so, and the magnitude of the fall is positively correlated with surgical severity. When bioavailable cortisol is estimated using the free cortisol index (FCI), we found little change in FCI with ‘Minor’ procedures, doubling of FCI with ‘Moderate’ surgery and tripling of FCI with ‘Major’ procedures. This suggests that the increase in bioavailable cortisol may be much larger than might be appreciated from looking at total serum cortisol. It may also explain the paradox of total serum cortisol levels falling to baseline levels in many patients on post-operative day 1: the free cortisol is likely to be higher than pre-operatively, given a fall in FCI and albumin levels after surgery. A true appreciation of the cortisol stress response to surgery will require a study which utilises validated methods for directly measuring free cortisol, for example equilibrium dialysis.

We found that the range of peak cortisol responses to ‘Major’/‘Major+’ surgery can vary widely, from 375 to 1452nmol/l in our dataset. Plumpton and Besser showed that in their cohort the cortisol range for their surgical procedures was higher by 30‒38% (equivalent to 607‒2070nmol/l). Whilst our hypoadrenal patients.’

Emotional stress is cited as a precipitant of adrenal crisis in a large number of patients, for example 1 in 6 in a survey of hypoadrenal patients.24 Unlike the model of surgical stress that has been used to develop our current guidelines, psychological stressors are difficult to standardise and have been less well studied.

Modelling mental stress in healthy volunteers can be done by looking at individuals during a stressful period such as important exams. A study of 36 Spanish medical graduates undertaking career-defining exams measured salivary cortisol during the preparation, exam and post-exam periods.11 Anxiety during the study in each individual was tracked using a validated questionnaire. The measured salivary cortisol was noted to be significantly increased during the exam period, compared with the post-exam period when anxiety scores had normalised.

Other studies have, however, not shown similar findings, and the variability in responses may be due to some extent to methodological issues, such as the use of different stressors and the measurement of salivary cortisol. The use of measurements of serum cortisol or plasma ACTH is much less common in this research sphere, but may provide more consistent results.12

At present, there are no recommendations on the management of psychological stress. Patients are not routinely advised that they should change their regimen during such periods, although, anecdotally, patients do often take extra doses.

Despite nearly 50 years of study, the cortisol stress response continues to be poorly understood in many ways. The current guidance for management of surgery in hypoadrenal patients that is available from different expert groups varies, with some advocating far higher doses of hydrocortisone than others.25 Further research into the physiology of stress is essential to develop the evidence base for the proper treatment of our hypoadrenal patients.

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REFERENCES
In three consecutive patient surveys, conducted 10 and then 5 years apart (2003, 2013 and 2018), we asked adrenal patients to list the trigger factors that had contributed to their previous episodes of adrenal crisis (Figure 1). The questionnaire offered a tick box list of prompted items, plus space to write comments.

Respondents in all three surveys were members of various adrenal support groups (Table). The average time since diagnosis was broadly consistent: 12.8 years in 2003, 12.2 years in 2013; 11.5 years in 2018. The 2013 and 2018 surveys were conducted online using Survey Monkey, while the 2003 questionnaire was distributed as a paper copy with a pre-paid return envelope. Here’s what patients reported.

In 2018, one in five adrenal patients checked the box to say that anxiety, bereavement or emotional stress had been a trigger factor for a previous adrenal crisis. That’s 94 of 477 replies, or 19.7%.

Five years earlier, in 2013, we asked the same question. There were small differences, but they were not statistically significant. Fifteen years earlier, in 2003, the question about causation had been worded less specifically, asking if ‘shock’ had been a trigger factor for a previous crisis. That’s 26.8 of 432 replies, or 6.1%.

Both disciplines concern themselves with diseases that influence cognitive functions, sleep pattern and appetite. Stress often seems to have a destabilising impact on a patient’s condition. Psychiatrists typically have no hang-ups about the role of emotional stress in destabilising their patients. Endocrinologists, on the other hand, tend to be a little prudish.

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Table. Adrenal support groups whose members took part in the 2003, 2013 and 2018 surveys.

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Over the same 15 years, daily hydrocortisone doses reduced appreciably, as many readers will be aware. While maintenance doses are now believed to be more closely aligned with ‘normal’ physiological values,4,5 this appears to leave patients twice as vulnerable to adrenal crisis when faced with infectious illness or surgical stress,6 and more than four times as vulnerable to adrenal crisis in emotionally challenging social situations. Patient survey findings suggest that the stiff upper lip just isn’t cutting it.

We must conclude that anxiety and emotional distress need to be taken seriously as destabilising factors with an adrenal safety risk, and newly diagnosed patients should be guided in the development of a tailored self-treatment plan for psychological upset.

KATHERINE G WHITE
Former Chair and Clinical Advisory Panel Co-ordinator, Addison’s Disease Self-Help Group

Katherine is currently studying towards a PhD and is available for small consultancy projects (kgwhite@mackaywhite.co.uk).

A SEISMIC SHIFT

That’s a major shift: 4.1-fold more patients reporting anxiety/emotional upset as a causal factor for adrenal crisis after a 15-year interval. The proportions reporting various other trigger factors also moved significantly, although by smaller ratios (Figure 1).

Over the same 15-year interval, the proportion of patients reporting a previous adrenal crisis also went up markedly. In 2003, over half of all respondents (54.5%) said they had never experienced an adrenal crisis post-diagnosis. That crisis-free cohort shrank to one-third of respondents (32.4%) by 2018 (Figure 2).

WHAT IS DIFFERENT?

So what has changed to destabilise adrenal patients? Are NHS endocrine units now so severely under-resourced that clinicians are neglecting patient education about sick day rules, perhaps?

We can discount that hypothesis because these datasets are wholly derived from patients belonging to an endocrine charity, the majority being members of the Addison’s Disease Self-Help Group. Over the 15-year period, the range of informational materials produced by the various adrenal charities has been considerable, and patient access to these materials through social media has transformed patients’ educational opportunities.3 By the time of the latter two surveys, the patients in these datasets were considerably better informed about the necessity for dosage adjustments and/or injected steroids in the event of intercurrent illness or major injury, when compared with those in 2003.

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So what has changed to destabilise adrenal patients? Are NHS endocrine units now so severely under-resourced that clinicians are neglecting patient education about sick day rules, perhaps?

We can discount that hypothesis because these datasets are wholly derived from patients belonging to an endocrine charity, the majority being members of the Addison’s Disease Self-Help Group. Over the 15-year period, the range of informational materials produced by the various adrenal charities has been considerable, and patient access to these materials through social media has transformed patients’ educational opportunities.3 By the time of the latter two surveys, the patients in these datasets were considerably better informed about the necessity for dosage adjustments and/or injected steroids in the event of intercurrent illness or major injury, when compared with those in 2003.

Over the same 15 years, daily hydrocortisone doses reduced appreciably, as many readers will be aware. While maintenance doses are now believed to be more closely aligned with ‘normal’ physiological values,4,5 this appears to leave patients twice as vulnerable to adrenal crisis when faced with infectious illness or surgical stress,6 and more than four times as vulnerable to adrenal crisis in emotionally challenging social situations. Patient survey findings suggest that the stiff upper lip just isn’t cutting it.

We must conclude that anxiety and emotional distress need to be taken seriously as destabilising factors with an adrenal safety risk, and newly diagnosed patients should be guided in the development of a tailored self-treatment plan for psychological upset.

KATHERINE G WHITE
Former Chair and Clinical Advisory Panel Co-ordinator, Addison’s Disease Self-Help Group

Katherine is currently studying towards a PhD and is available for small consultancy projects (kgwhite@mackaywhite.co.uk).

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Thank you to all who attended the HRA Pharma-sponsored satellite symposium

Challenging cases in Cushing’s syndrome: Approaches and Management

We look forward to next year
GLUCOCORTICOIDS: RESTORING BALANCE DURING STRESS
WRITTEN BY GIORGIO CARATTI, PAULINE PFÄNDER & LAURA MATTHEWS

While we often associate the term ‘stress’ with anxiety, the term really encompasses any challenge that has potential to disrupt homeostasis. This includes physical stressors like infection or injury. The physiological requirements in response to these diverse challenges are all mediated – at least in part – by the glucocorticoid cortisol.

PHYSIOLOGICAL EFFECTS
Glucocorticoids are cholesterol-derived steroid hormones synthesised and secreted by the adrenal gland. They are anti-inflammatory in all tissues, and control metabolism in muscle, fat, liver and bone. Glucocorticoids also affect vascular tone, and in the brain influence mood, behaviour and sleep-wakefulness cycles.

Glucocorticoid excess (due to pathology such as Cushing’s syndrome or prescribed synthetic glucocorticoids) can cause immunosuppression, muscle atrophy, central adiposity, hepatosteatosis, osteoporosis, insulin resistance, hypertension, depression and insomnia.

Elevated glucocorticoids can therefore be damaging, and so their production is under the strict control of the hypothalamic-pituitary-adrenal (HPA) axis (Figure 1). Activation of the hypothalamus initiates the release of corticotrophin-releasing hormone (CRH), which in turn signals to the anterior pituitary to release ACTH, which then signals to the cortical layer of the adrenal gland to release cortisol (CORT), which can act on peripheral tissues. Over time, elevated circulating cortisol feeds back to the hypothalamus and pituitary to block further release of CRH and ACTH respectively, which inhibits further cortisol release.

MAINTAINING BALANCE
In the context of maintaining normal homeostasis, the daily peak of glucocorticoid is very important. The transient peak increases vascular tone and alertness, mobilises energy and has a priming effect on the immune system. Essentially, your morning dose of cortisol prepares you to face the potential challenges in your day.

Stresses encountered through the day can drive additional pulses of glucocorticoids from the adrenal which drive sustained, elevated glucocorticoid levels. This produces the same physiological response but with a greater magnitude. In a ‘fight or flight’ context for example, glucocorticoids increase vascular tone and alertness, mobilise energy (prepare you to run) and prime the immune system (prepare you for injury). These preparatory effects increase the likelihood that the stressor can be overcome, so that normal homeostasis can be quickly restored.

It seems paradoxical that a potent immunosuppressive hormone would prime the immune system, but facilitating activation of immune cells is beneficial. It increases the ability of the immune system to detect pathogens/injury and respond accordingly, and it facilitates resolution and repair, to restore balance. In the context of chronic infection or disease, however, the role of glucocorticoids changes, in order to prevent escalation and limit damage.

continued on page 20…
Glucocorticoids act directly on cells within the damaged tissue to block production of inflammatory signals (cytokines, chemokines) that attract immune cells. They act directly on the immune cells to inhibit their ability to infiltrate the tissue, and in some cell types induce their death. Glucocorticoids also promote activation of scavenger immune cells that help remove cell debris, promote repair and prevent lasting damage (such as fibrosis). At the cellular level, glucocorticoids are able to control metabolism, inflammation, adhesion, migration and survival, in a cell-specific and context-specific manner.

**MECHANISM OF ACTION**
Glucocorticoids mediate their cellular effects through binding and activating the glucocorticoid receptor (GR), which is expressed in almost every tissue. Glucocorticoids diffuse into the cell, and bind and activate the GR, which then moves into the nucleus.

The GR can bind DNA directly at specific glucocorticoid response elements (GREs), and then recruit coactivator or corepressor proteins to increase or decrease expression of target genes. The GR can also bind or tether itself to other DNA-bound transcription factors and modulate their ability to change gene expression (Figure 2).

The specific genes that the GR can control—and therefore the cellular processes that glucocorticoids can regulate—are critically determined by the ability of the GR to bind. This adds an additional layer of control, because gene accessibility and transcription factor expression and activity are cell-specific and dynamically regulated.

For example, liver-specific transcription factors such as HNF4 (hepatocyte nuclear factor 4) facilitate GR binding to (and regulation of) metabolic genes, whereas macrophage-specific transcription factors such as PU.1 recruit GR to genes important in immunity.

Glucocorticoid responses are therefore fine-tuned to consider context. This is how glucocorticoids can control metabolism in liver, activation of macrophages, and promote death of T-cells.

The GR is also recruited by the proinflammatory transcription factor NFκB (nuclear factor-kB). In contrast to HNF4 and PU.1, NFκB is expressed in every cell, but only binds DNA when activated in response to a pathogen or tissue damage. Consequently, the GR is only recruited to (and inhibits) proinflammatory genes if NFκB is activated. This explains why the GR (and glucocorticoids) is a potent inhibitor of inflammation only when required: i.e. when inflammation is already present.

Glucocorticoids (through the GR) are therefore perfectly adapted to integrate incoming signals from other pathways in order to respond appropriately to each specific challenge. We still have a long way to go in order to fully understand the whole spectrum of glucocorticoid action. However, we now have some insight into how, by adding a few additional points of control, glucocorticoids can co-ordinate diverse cellular effects to reach a common goal: the restoration of balance following stress.

Risk-taking is a fact of life—but just how much risk we are prepared to contemplate as an individual varies enormously. If the trickiest decision of the day is whether to take your raincoat or not, then you probably aren’t in the same collective group as the so-called ‘rooftoppers’ or other ‘urban explorers’, whose antics on high-rise buildings make for eye-popping pictures (check out Kirill Oreshkin, pictured above, the Moscow-based ‘Russian Spiderman’).

Of course, risk-taking by others can have a dramatic impact on our own lives. It’s just over a decade since the financial crash of 2008, an event with ramifications that continue to reverberate around the globe. At the heart of the downturn was a misplaced optimism/belief that prosperity could continue unabated. Bankers in particular (many of whom had only ever experienced the good times) had grown over-confident.

**FINANCIAL SUCCESS**
Success in the financial markets is dependent on various traits, of which preparedness to take risks is a key one. Classical economic/finance theory postulates that we make consistent choices, based on our risk preferences, which remain relatively stable over time. Accordingly, for the most part, we therefore make rational choices.
However, even prior to the crash, some workers (including an extra-
drier, Dr John Coates) had come to question these beliefs, pointing
out that traders often seem prepared to take increasing risks during a
market bubble, but become more risk averse when the markets are in
decline.

**AN ENDOCRINE BASIS**

So how does endocrinology fit in to this? The first thing to say is that
currently there is a paucity of ‘real life’ data in relation to female
traders, and therefore what follows is a summary of findings from
studies predominantly involving male traders – all of which raises the
intriguing and important question as to whether a more gender-balanced
environment might yield different outcomes.

In brief, evidence from studies conducted in the field (on real trading
floors) and in the laboratory (with volunteers incentivised to take risks to
generate profit) has raised the possibility of a ‘winner effect’, in which
success and rising testosterone levels go hand in hand, one driving the
other. So during individual winning streaks, and more broadly during
bubbles (i.e. market-wide winning streaks), traders make above average
profits. Success is associated with increased testosterone levels which, in
turn, increase risk appetite and the size of individual trades.

However, at some point, traders become over-confident, placing bets of
ever-increasing sizes, with increasingly adverse risk–reward trade-offs, until
eventually things go wrong and they suffer significant losses (an inevitable
consequence of what is often referred to as prior ‘irrational exuberance’)
(see Figure). During financial crises and market crashes, the same traders
suffer losses on a scale greater than anything they could have imagined.

**WHEN STRESS ENTERS THE SCENE**

At this point, life becomes stressful. Traders face the prospect of losing
their job, personal bankruptcy and the social stigma of having to curtail
the lavish lifestyle that accompanied their increased wealth, resulting from
the prior bubble.

I can already hear the cries of ‘Serves them right!’ ‘It wasn’t even their own
money they were taking risks with…’ and ‘We have all ended up paying for
their errant ways.’ However, perhaps we should care about traders who are
stressed, because emerging evidence suggests that a stressed trader is not
what you need when the going gets tough.

Chronic stress has both physical and psychological consequences. The
latter include impaired attentional control and behavioural flexibility.
Raised cortisol also promotes anxiety, a selective recall of disturbing
memories, a tendency to find danger where none exists, and even depression and learned helplessness.

It doesn’t take much of a conceptual leap, therefore, to imagine just
how chronically elevated cortisol levels might have an impact on a
trader’s behaviour. Indeed, data collected from traders in the City of
London during periods of high market volatility and uncertainty show a
remarkable correlation between indices of market volatilised and traders’
endogenous cortisol levels. Furthermore, in laboratory studies examining
the effects of raised cortisol (comparable with the levels observed in the
traders) on risk-taking behaviour, even modest hypercortisolism was found
to significantly change risk preferences, with a demonstrable increase in
risk aversion.

**CONFOUNDING PREVIOUS IDEAS**

So, it seems that existing economic/finance models in which risk
preferences are a fixed trait (in much the same way as eye or hair
colour) may not hold true after all. Instead, the behaviour of traders is
susceptible to external influences that interact with the body’s
systems (including its endocrinology), and therein bring about a chain
of unanticipated events.

Once a market bubble bursts and a bear market ensues, increasing
uncertainty and volatility raise levels of stress amongst traders. If
sustained, the result will be market uncertainty and volatility
raise cortisol levels. As this stress response persists and becomes chronic,
the cortisol promotes risk aversion and the irrational pessimism that
pushes a bear market into a crash.

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DI: A DANGER OF INCOMPETENCE?

WRITTEN BY STEPHANIE E BALDEWEG

Do you remember a clinical situation where your patient with diabetes insipidus (DI) was admitted to hospital and did not get their desmopressin or fluids as needed? Or one where they were admitted to hospital and were offered a drug they did not need (usually metformin) for their diabetes?

If you do not recall such a situation, I challenge you… Think harder or listen to your patients with DI, most of whom can report this from first-hand experience.

A CASE OF NEGLECT

Diabetes insipidus is distinguished from diabetes mellitus (DM), which describes polyuria with sweet urine. However, gradually, the word ‘diabetes’ has become synonymous with ‘diabetes mellitus’ in most lay and non-endocrine medical arenas.

The problem of ‘DI’ terminology is painfully illustrated by the tragic and avoidable death in 2009 of a 22-year-old man, who was admitted to a London teaching hospital for an elective hip replacement. He was fit and well but required full pituitary replacement therapy, including desmopressin, after treatment for a suprasellar germinoma the previous year. Treatment for the germinoma with high dose glucocorticoid therapy had caused avascular necrosis of his hip.

On admission to the orthopaedic ward, his drug chart was completed with the appropriate pituitary hormone replacement therapy, including desmopressin, but the endocrine team was not informed. He was not given the desmopressin or access to free fluids. He was reviewed by a psychiatrist with the appropriate pituitary hormone replacement therapy, including desmopressin, after treatment for a suprasellar germinoma the previous year. Treatment for the germinoma with high dose glucocorticoid therapy had caused avascular necrosis of his hip.

The next morning, the patient had a fatal cardiac arrest with a serum sodium of 136mmol/L. The coroner’s inquest highlighted the failure to inform the endocrine team on admission and concluded that neither the doctors nor nurses nor pharmacists on the ward understood the complexity of the patient’s medical condition. No desmopressin had been administered to the patient for 48 hours since his admission. The coroner summarised that the death was due to ‘dehydration contributed to by neglect’. The legal case for this young man ended in 2012.1

‘Gradually, the word “diabetes” has become synonymous with “diabetes mellitus” in most lay and non-endocrine medical arenas.’

TAKING ACTION

In February 2016, NHS England sent an alert to all doctors informing them of the risk of omitting life-sustaining medication.2 It quoted evidence from NHS England and from the National Reporting and Learning System (NRLS) that from 2009 to 2015 there had been 471 incidents involving desmopressin. Of these, the wrong dose (n=56) and omission (n=76) were the commonest errors. Four of these omissions had resulted in death from severe dehydration. The NHS alert recommended that measures be put in place in all hospitals to ensure patients received their life-sustaining therapy.

So, this sounds all rather dangerous and concerning. What can we do?

FLAGGING AND ALERTING

One means to avoid this catastrophe is an educational programme in all hospitals. Where electronic prescribing systems are used, a mandatory flag should be in place for desmopressin with warnings that it is a life-sustaining therapy and must never be omitted, and supplies must be obtained immediately, or a doctor called. This is similar to alerts for all steroid and insulin prescriptions.

EMPOWERING THE PATIENT

A parallel route is to educate and empower the patients. The Pituitary Foundation, the national UK charity for patients and carers with pituitary disease, provides detailed information on DI as well as an alert card for patients to carry and show to their doctors.3 The Pituitary Foundation’s Awareness Month campaign in October 2018 focused on DI, suggesting a number of ways to raise awareness of the condition.4

GUIDELINES FOR EMERGENCY TREATMENT

Thirdly, we (the Society for Endocrinology’s Clinical Committee) have published simple and effective emergency guidelines for the treatment of cranial DI in in-patients.5 This information is freely available on the Endocrine Connections website and also disseminated via The Pituitary Foundation and the Society’s Endocrine Networks. Please distribute the guidelines in your institutions. As part of The Pituitary Foundation’s Awareness Month campaign, the guidance has also been shared with patients, who are encouraged to show the information to their treatment team at every admission.

CHANGING THE NAME

Avoiding the word ‘diabetes’ would be another way to reduce the chance of staff failing either to recognise DI or to distinguish it from DM. Whilst endocrinologists find no problem with the term DI, there is clear evidence of confusion and treatment failures, as highlighted in the safety alert. Renaming DI would help to inform healthcare professionals and patients alike that this is a condition requiring specialist life-sustaining therapy which is distinct from DM. It would emphasise the need to continue therapy in all situations with the assistance of endocrine teams. This approach is strongly supported by The Pituitary Foundation and advocated in a recent commentary by Malcolm Prentice.6

If you, like me, enjoy reading The Endocrinologist as ‘light relief’ on the train/away from your office, I urge you to keep this article and, when you are back in the office, consider how safe the patients with DI in your hospital are, and what else you will do to make them safer.

STEPHANIE E BALDEWEG

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Honorary Senior Lecturer, Department of Medicine, UCL
Department of Diabetes & Endocrinology, University College London NHS Foundation Trust
Trustee, The Pituitary Foundation

REFERENCES
NEW IMPROVED WEB ACCESS
Brand new websites for Society journals means that you can access cutting-edge research and best practice in endocrinology even more easily. You will find links to the new sites for Journal of Endocrinology, Journal of Molecular Endocrinology, Endocrine-Related Cancer, Endocrine Connections and Endocrinology, Diabetes & Metabolism Case Reports at www.endocrinology.org/publications.

The new websites incorporate great new features to help you easily and conveniently keep up to date with the latest endocrine research and clinical practice. From topic-based collections to the ability to highlight and comment on articles, these websites have everything you need in one place to simplify and personalise your endocrine reading.

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From January 2019, Clinical Endocrinology will be available to members to read online only. As well as significantly reducing the carbon footprint associated with printing and mailing, this transition, together with the introduction of the free app, means you can access the latest research published in the Society’s clinical journal anytime, anywhere.

Never miss an issue – sign up for free email alerts on the Clinical Endocrinology homepage and download the app from iTunes.

DON’T MISS THESE SPECIAL ISSUES

**Sulfation pathways**
Journal of Molecular Endocrinology
*Volume 61 | Issue 2 | August 2018*

Learn more about our current understanding of steroid sulfation pathways and their interaction with endocrine systems in this special issue, which comprises 10 research and review articles, with an editorial by Jon Wolf Mueller and Paul A Foster (see doi.org/10.1530/JME-18-0109).

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Endocrine-Related Cancer
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Containing 7 thematic reviews by leaders in the field, this issue marks 65 years since Watson and Crick published the structure of DNA’s double helix. It includes an editorial by William Foulkes, Jérôme Bertherat and Charis Eng (see doi.org/10.1530/ERC-18-0283).

SOCIETY NEWS

Alison Milne: **2019 ENDOCRINE NURSE AWARD WINNER**

We congratulate Alison Milne, Endocrine Nurse Specialist at NHS Grampian’s JJJR Macleod Centre for Diabetes and Endocrinology in Aberdeen, who has been announced as the winner of the Society’s Endocrine Nurse Award for 2019.

Alison was chosen in recognition of her exceptional work in running The Pituitary Foundation Endocrine Nurse Helpline for 10 years. The Society’s Endocrine Nurse Award aims to recognise individuals who have demonstrated innovative and successful nurse-led initiatives in the endocrine field that have advanced best practice in research, education or patient care.

Alison said, ‘This helpline is a valuable service for patients, their families and carers who have been diagnosed with a pituitary condition. These are very rare and complex conditions and people feel very isolated and alone. Many hospitals in the UK do not have the luxury of a specialist endocrine team and have no specialist nurse to advise them. This is why I feel that my Nurse Helpline was so valuable and so much in demand.’

The judges who made the Award to Alison emphasised the importance of her work in supporting patients: ‘The Helpline is an indispensable resource for patients and is clearly used widely across the UK. Alison has demonstrated the positive impact it has had on patients and it is clear it is much needed. Alison has been key in the development and success of this service. Alongside this, she has developed a great resource document for patients post-surgery, and she continues to champion the Endocrine Specialist Nurse role for patient support.’

They added, ‘Her commitment over a 10-year period to The Pituitary Foundation, her innovations in steroid education and her dedication to patient care are to be celebrated. She deserves this award.’

If you have a nurse colleague whom you would like to nominate for the Society’s 2020 Endocrine Nurse Award, remember that applications are now open until 8 July 2019. See www.endocrinology.org/grants-and-awards/prizes-and-awards/endocrine-nurse-award for further details.

The latest from your SOCIETY JOURNALS

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Your new GENERAL SECRETARY AND PROGRAMME SECRETARY

Eleanor Davies and Duncan Bassett began their terms of office at the recent Society for Endocrinology BES conference. Each brings a wealth of knowledge and enthusiasm. Here, they tell us about their careers so far, and what they are looking forward to most about their new roles.

An interview with…

ELEANOR DAVIES
SOCIETY GENERAL SECRETARY

Eleanor Davies is Professor of Molecular Endocrinology at the British Heart Foundation Glasgow Cardiovascular Research Institute. She specialises in translational research into the role of aldosterone in cardiovascular disease. She has previously been a member of the Society’s Programme and Science Committees.

WHAT DREW YOU TO BECOME INVOLVED IN ENDOCRINE RESEARCH?
At school I was very keen on languages. I wanted to do chemistry, biology, French and German, but this was impossible to fit into the school timetable, so I chose chemistry, physics and biology. I was interested in the mechanisms of disease and, looking back, I should have applied to do medicine. However, I was squeamish at school, and the thought of anatomy filled me with dread, so I did a degree in biochemistry at the University of Glasgow.

During my final undergraduate year, I applied to do a project on breast cancer but it was oversubscribed. Instead, I was allocated a project with Robert Fraser and Chris Kenyon at the MRC Blood Pressure Unit in Glasgow. It was on the role of calcium ions in steroid production by the adrenal gland. I really enjoyed it and got my first publication, which was a nice bonus. Presenting the work at the Society for Endocrinology BES conference in Leeds was my first introduction to the Society and all things endocrine; I really enjoyed the conference and the diversity of the subject area. My main memory was being introduced to James and Sylvia Tait, who had discovered aldosterone. This obviously made a lasting impression, as I've been working on aldosterone and its role in cardiovascular disease ever since!

WHAT INDIVIDUALS HAVE INSPIRED YOU MOST?
I've been really fortunate to have worked in some great laboratories, with many people who have been extremely supportive of my career. I undertook my PhD in Edinburgh with Brent Williams and Sir Christopher Edwards. After that, I worked in Paris with Eric Clauser and Pierre Corvol, before I returned to Glasgow and worked with John Connell and, once again, with Robert Fraser. All these people have been a great support to me. They have been instrumental in shaping my career and developing my interest in cardiovascular endocrinology. Along the way, I've made some great friends around the globe. This is really the most enjoyable part of my job.

WHAT DO YOU VIEW AS YOUR GREATEST ACHIEVEMENTS SO FAR?
I'm always proud to see my students and postdocs do well and progress in their careers; this is really rewarding.

I'm from a working class background and was the first person in my family to go to university, so I'm pleased to have made it to professor. My Dad asked me at my professorial inauguration lecture, ‘Is this quite an important thing?’. It’s always good to keep both feet firmly on the ground!

WHAT IS THE BEST THING ABOUT BECOMING GENERAL SECRETARY?
Having been a member of the Society all my working life, and having attended almost all the annual conferences, it’s nice to see how the Society has grown and evolved to be the vibrant, successful operation that it is today. I’m very pleased to be involved in shaping the direction and future of the Society, so that it serves our membership and stakeholders in the best way possible.

WHAT WOULD YOU LIKE TO SEE HAPPEN WHILE YOU ARE IN THE ROLE?
I want to promote endocrinology and ensure we attract as many people as possible into our discipline, and into the Society. I’m particularly passionate about supporting our early career researchers and helping them succeed in their chosen career path.

WHAT OBSTACLES FACE US AS ENDOCRINOLOGISTS, AND HOW CAN WE SUPPORT THE FUTURE OF OUR DISCIPLINE?
I think Brexit will present a challenge to the Society, our members and the scientific/clinical community at large, as we rely on scientific collaboration and mobility.

I would like to see a more stable career structure for our basic scientists and greater investment in creating fellowships and tenured posts. Investing in our early career researchers is key to maintaining the future of research in endocrinology.

WHAT ARE YOUR INTERESTS WHEN YOU AREN’T AT WORK?
My daughter has just left home to go to university, so I have a bit more time on my hands. In the last year I've taken up skiing. It's probably not my best idea, so expect to see me in plaster sometime soon! I'm also contemplating taking piano lessons, although I'm not sure I have the patience to learn all the scales.

WHAT WOULD YOU SAY TO SOMEONE STARTING OUT IN ENDOCRINOLOGY?
Enjoy your research and take as many opportunities as you can, go to new places and learn new things. The world is a big place; go and enjoy it!
An interview with...

DUNCAN BASSETT

SOCIETY PROGRAMME SECRETARY

Duncan Bassett is Professor of Endocrinology at Imperial College London and a Consultant Physician at the Academic Health Sciences Centre, where he specialises in metabolic bone disease. He has previous experience as a member of the Society’s Programme and Science Committees, and is a former Society Bone and Calcium Endocrine Network convenor.

Q WHAT INSPIRED YOU TO DO RESEARCH, AND WHY ENDOCRINOLOGY?

Most of all, I enjoy the intellectual freedom of designing, performing and analysing experiments. It’s great fun and addictive: once you get started, it is very hard to stop. There are always new questions and challenges to keep me interested.

I first became fascinated with endocrinology when I was a Senior House Officer at the Hammersmith Hospital in London, and I met a family with multiple endocrine neoplasia type 1 (MEN1). It was such a remarkable and complex disease that I knew immediately I wanted to try and understand its pathogenesis.

Q WHO HAVE BEEN YOUR MENTORS?

David Weatherall was a key influence when I was a clinical student. He encouraged me into laboratory research and, crucially, introduced me to Kay Davies, in whose laboratory I discovered my love of genetics and molecular biology. I will always be grateful to both of them for the opportunities that they gave me. After I specialised in endocrinology, Raj Thakker supervised my PhD on the genetics of MEN1 and was instrumental in helping me to establish a career as a clinical academic.

But, perhaps most importantly, I am grateful to Graham Williams, the current President of the Society, with whom I have worked for 15 years to establish and develop a laboratory focused on the skeletal actions of thyroid hormone and, more recently, the genetic basis of bone and cartilage diseases.

Q WHAT, SO FAR, ARE YOU MOST PROUD OF IN YOUR CAREER?

There are two current projects which I think will have important benefits for the field and will open up new opportunities to study the role of thyroid hormone in development, metabolism and repair in many different T3 target tissues.

In addition, to investigate the genetic basis of osteoporosis and osteoarthritis, and as part of the International Mouse Phenotyping Consortium, we have developed rapid-throughput bone and joint phenotyping platforms. To date, we have phenotyped nearly 1000 knockout lines, identifying many new genes involved in bone mass and strength, and functionally annotating the most recent UK Biobank genome-wide association studies. These studies will inevitably lead to better patient diagnosis and care in the future.

Q WHAT EXCITES YOU MOST ABOUT BEING PROGRAMME SECRETARY?

I’m committed to bringing the best cutting-edge clinical, basic and translational research to the Society for Endocrinology BES conference. I think it is important to highlight major new national and global research initiatives and to present opportunities for these resources, technologies and approaches to be incorporated into endocrinology. I’m also passionate about inspiring the next generation, by demonstrating the breadth and significance of endocrinology in the conference programme.

Q WHAT DO YOU HOPE TO ACHIEVE DURING YOUR TERM?

I really want to encourage a greater number of higher quality and diverse suggestions for the Society for Endocrinology BES conference programme. I hope to ensure that the programme is even more inclusive, and covers all key interest groups. To this end, I am also keen to strengthen the range of expertise on the Programme Committee, to make sure we have clinical and basic representation from all areas. My focus will be on inviting world-leading speakers from overlapping fields who are pioneering innovation. I think it is important for us as endocrinologists to challenge ourselves, to get out of our comfort zone and to embrace new technologies and approaches.

Q WHAT ARE THE BIGGEST CHALLENGES IN ENDOCRINOLOGY, AND HOW MIGHT THEY BE RESOLVED?

I think for endocrinology to survive and prosper as an independent field, it needs to become broader and cross-cutting, encompassing the whole of intercellular signalling. We need to challenge ourselves and look for new long term opportunities to ensure its viability as a discipline.

Q WHAT DO YOU ENJOY DOING OUTSIDE OF WORK AND ENDOCRINOLOGY?

I’m much too busy for that! When I do have the time, I enjoy cooking, painting, building bikes and cycling in the Surrey hills.

Q WHAT WORDS OF WISDOM DO YOU HAVE FOR ASPIRING RESEARCHERS?

I always think getting hands-on experience of laboratory research as early as possible is the key. Pursuing a research career today is certainly a challenge and, to be successful, you almost need to feel that you can’t live without it. This means you need to love laboratory life and find a subject that really fascinates and excites you. It is the passion that will sustain you through the hard times and will come across in grant applications and interviews, helping you to get funded. Finally, it is really important to identify someone who will help you during your early career. We have all had difficult moments in our careers where such support, advice and guidance have been invaluable, especially in terms of new opportunities, collaborations and funding.
New UK survey: SEVERE SIDE-EFFECTS OF ANTI-TYROID DRUGS

Anti-thyroid drugs (ATDs) are the main treatment modality for many patients with hyperthyroidism, which affects about 2% of women over a lifetime.

In the UK, about 15,000 new patients are treated with ATDs each year: most receive carbimazole and some have propylthiouracil. About 1 in 500 of these patients will develop agranulocytosis (a serious condition with very low white blood cell count) as an idiosyncratic adverse drug reaction. Although this reaction typically occurs between 4 and 6 weeks after starting to take an ATD, it may occur at any time during treatment.

Patients with agranulocytosis are often critically ill. This requires high dependency care and sometimes results in death. Indeed, a previous study of 203 patients with ATD-associated agranulocytosis whose cases were reported to the UK Committee for Safety of Medicines (CSM) between 1964 and 2003 found a mortality rate of 10%.

As well as agranulocytosis, fulminant hepatotoxicity has also emerged as an important life-threatening adverse effect of ATD, particularly associated with propylthiouracil use. Although it is also a rare adverse reaction, with an incidence of 1 per 1000 patient years, 10% of patients with this adverse reaction will suffer from liver failure, leading to liver transplantation or death.

THE NEED FOR A NEW STUDY

Due to the rarity of the ATD-associated agranulocytosis and fulminant hepatotoxicity, any one clinical team manages only a handful of cases over several years. Therefore, a systematic examination of these ATD-associated serious adverse reactions has been difficult. The previous large UK study was based on voluntary reporting of the adverse effects to CSM via the yellow card scheme between 1964 and 2003. However, a major limitation of the study is the incomplete ascertainment of data in many yellow card reports.

AIMS AND OBJECTIVES

Using the Society for Endocrinology Thyroid Endocrine Network, we plan to conduct a systematic survey of contemporary UK patients. These individuals will have suffered with ATD-associated agranulocytosis or fulminant hepatotoxicity in the last 10 years (retrospective cases), or will be identified in the clinic over the next 2 years (prospective cases).

We aim to document the demographic and other risk factors for these adverse reactions and examine any beneficial or deleterious management strategies. We will use a systematic questionnaire to elicit information regarding demographic details, ethnic background, concomitant drug use, latency and duration of reaction, full blood indices (including neutrophil counts), presence of fever, site of any focal infection, cultured organisms and clinical outcome for patients with ATD-associated agranulocytosis. In addition, we will document the use of blood transfusion and haematopoietic stimulating factors (for example, granulocyte–macrophage colony-stimulating factor, GM-CSF). For patients with hepatotoxicity, we will collect clinical details, including serum liver enzymes, actual liver transplantation, patient ‘listing’ for transplantation and outcome of hepatotoxicity.

Like many other idiosyncratic drug reactions, it is likely that ATD-associated agranulocytosis and fulminant hepatotoxicity are due to one or more rare genetic variants that predispose the patient to these adverse effects. Therefore, we also aim to obtain DNA samples from the affected patients for future genetic studies, in order to identify associated rare genetic variants.

This systematic and detailed study of rare cases of ATD-associated agranulocytosis and severe hepatotoxicity will provide an invaluable research resource to identify individuals at risk of these adverse reactions and to improve patient safety.

This project is generously funded by the Clinical Endocrinology Trust, and the Society for Endocrinology is providing study management and co-ordination. We are in the process of seeking Health Research Authority approval and National Institute for Health Research clinical research network adoption.

COULD YOU CONTRIBUTE?

If you (or your centre) are interested in contributing to the study, please contact:

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BIJAY VAIDYA on behalf of the ATD Study Group
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I also gained experience at the Royal London Hospital, University College London Hospital, King’s College Hospital and, finally, Great Ormond Street Hospital. I gained an interest in growth and puberty disorders, adrenal disorders, neuroendocrine late effects of childhood brain tumours, and also disorders of sex development.

During this time, I worked with a group of paediatric nurses to develop the Royal College of Nursing Competencies: an Integrated Career and Competency Framework for Children’s Endocrine Nurse Specialists. This followed the introduction of the Agenda for Change, when more nurses were having to justify their roles to managerial structures. It proved a success when it was launched in 2008, and the adult endocrine nurses followed on swiftly with their Competency Framework for Adult Endocrine Nursing in 2013 and then 2015, in which I was lucky to also be involved.

THE MOVE TO EDUCATION
In September 2015, I made the huge decision to move from clinical practice into higher education for children’s nurses. I had always enjoyed the teaching and presenting part of my role. This ranged from teaching patients and their families to teaching ward staff, and included involvement at national and international conferences. These spanned British Society for Paediatric Endocrinology and Diabetes (BSPED) meetings, Society for Endocrinology BES conferences and Endocrine Nurse Updates, ENDO meetings and the Pediatric Endocrinology Nursing Society (PENS) conferences.

I thought that these experiences would serve me well, but I was not prepared for the huge learning curve I was about to encounter. It is one thing presenting to a large international conference, full of people interested in your expert opinion and knowledge – it is very different trying to teach first year undergraduate student nurses, many of whom were not born when I first qualified!

I found myself joining the teaching and marking teams for the modules ‘Communicating with children and young people’, ‘Public health’ and ‘Health promotion’, amongst others. Eventually, word spread around the department regarding my clinical expertise. I was then involved in teaching third year pre-registration nurses about steroids and insulin, helping design questions on reproduction and the stress response for the first year anatomy and physiology exams, and teaching growth and pubertal assessment for the post-registration ‘Advanced assessment’ module. Finally, the arrangements became more settled and I ran the PGDip ‘Anatomy and physiology’ module, and the ‘Applied clinical physiology’ post-registration module, as part of the MSc/PGDip Children’s Advanced Nurse Practitioner pathway, of which I am also now Course Director.

EXPANDING HORIZONS
It all sounds removed from my clinical days, but teaching the clinical side of things to students ensures I read up on the subject, and present best clinical practice with up to date recent research.

I am now involved in teaching many post-registration modules, including ‘Mental health in children and young people’, exploring clinical issues in paediatric endocrinology which can affect mental health. These include poor growth or early/delayed puberty, which can lead to bullying, and the impact of new diagnoses and learning coping mechanisms.

Other modules include ‘Children’s and young people’s cancer’, where I discuss long term endocrine late effects, and also ‘Children’s neuroscience’, where I teach about pituitary tumours and, of course, diabetes insipidus.

The most relevant post-registration module that I now lead is the BSc/MSc level module ‘Principles of care of the child and young person in endocrinology’, which has now had two successful intakes, and will next run in January 2020. It involves 6 intensive study days, where students are taught by clinical experts from across the UK on all topics in paediatric endocrinology. The BSPED has supported student attendance. Assessment is formative and summative. Summative assessment relates to the final mark, and the students have to give a case study presentation, which has resulted in some fascinating discussions on congenital hyperinsulinaemia, early puberty, disorders of sex development and growth hormone deficiency, amongst many others. The formative assessment is more of a group work exercise, where students worked in pairs on given scenarios, discussing the indications for growth hormone therapy and the arguments for various growth hormone delivery devices, the results of which were presented in poster format at the 2017 BSPED meeting in Newcastle and Gateshead.

REFLECTING ON THE TRANSITION
The transition into academia has not been easy. I have had to study for my Postgraduate Certificate in Practice Education, and am now on the ‘Nursing and Midwifery Council Register as a Nurse Teacher, so I am more au fait with curriculum planning and design. I also completed my Children’s Advanced Nurse Practitioner Postgraduate Diploma, squeezing in those last few required practice placement hours when I could.

The marking season can be heavy, with a multitude of essays (I once had 80 to get done in 2 weeks), case study presentations, OSCEs (objective structured clinical exams) and exams to mark. However, we, as the team, always make time for ‘reflection’ at the end of marking season!

My role has now taken me into the Non-Medical Prescribing team at London South Bank University, to be the Cohort Lead for the country’s only paediatric Non-Medical Prescribing course – please do contact me if you’re interested (email kate.davies@lsbu.ac.uk).

I do miss my clinical days sometimes, but if anyone is thinking of making this giant leap from the clinics to the classroom, I can wholly recommend it. I still think of myself as an endocrine nurse, but now as a teacher too!

KATE DAVIES
Senior Lecturer in Children’s Nursing/Non-Medical Prescribing, Children’s Advanced Nurse Practitioner, Department of Advanced and Integrated Care, London South Bank University

REFERENCES
NURSES’ NEWS

LISA SHEPHERD
NURSE COMMITTEE CHAIR

Nursing is a career that offers numerous opportunities, including things we may not initially consider when we first undertake our training.

As a student, we have preconceived ideas of what we will enjoy, and perhaps of which specialties we would like to work in. With time and experience, our view may change. Even when qualified, we may find ourselves moving specialties.

However, when I found myself reflecting upon this recently at the Society for Endocrinology BES conference, I noticed that a significant proportion of nurses have worked in endocrinology for more than 10 years. Endocrinology provides many opportunities and variety within the specialty.

Our discipline allows nurses to develop clinical or academic interests – or both. Consequently, few nurses leave the field, instead just changing hospital or developing their role.

I thank Kate Davies for her article in this issue (p. 29), which describes her journey from qualifying as a paediatric nurse to her role in academia. Her story demonstrates how transferable her skills as a nurse are, and how her previous experience in endocrinology continues to be utilised on a daily basis.

This is my last editorial as Chair of the Nurse Committee. I have thoroughly enjoyed my time in this role and we have made fantastic progress during my term of office. I thank the Society for Endocrinology, Council and the Officers for all their support and commitment in the development and advancement of endocrine nurses. I know this work will continue and grow, as I hand over to our incoming Chair, Anne Marland (Oxford).

I wish you a very Merry Christmas and a Happy New Year, and look forward to endocrine nursing practice continuing to flourish in 2019.

BEST WISHES
LISA SHEPHERD

bioScientifica
FOCUS
events

Obesity Update 2019
Thursday 14 February 2019 - Royal College of Physicians, London

ADVANCING KNOWLEDGE

Obesity Update 2019 is the ideal forum to share and learn from current obesity-related research and clinical practice. By attending you will advance your knowledge of obesity and have the opportunity to build relationships with clinicians and researchers working in the field.

96% of attendees said the 2018 meeting met their training and development needs.

YOUR RESEARCH, YOUR CHALLENGES

Submit your abstract to Obesity Update 2019 and expose your work to experts from across the UK.

You can gain valuable feedback, to help progress your work and raise your profile amongst your peers, further increasing opportunities to collaborate.

Find out more at www.obesityupdate.org

ENDORSED BY: Society for Endocrinology ASO

EARLY BIRD REGISTRATION DEADLINE:
Tuesday 15 January 2019
Events & Training 2019

Our events provide unique training opportunities and allow you to network with endocrine professionals from across the discipline.

Find more information at: www.endocrinology.org/events

National Clinical Cases
Royal Society of Medicine, London
12 MAR

The National Clinical Cases meeting will showcase ten oral communications selected from high scoring submitted cases. It provides an ideal forum for trainees to present clinical cases to peers and established endocrinologists.

Endocrine Academy
Clinical Update & Endocrine Nurse Update
Hilton Birmingham Metropole Hotel, NEC, Birmingham
8-10 APR

Endocrine Academy brings together Clinical Update (8 - 10 April) and Endocrine Nurse Update (8 - 9 April). Clinicians will benefit from essential training for the Royal College of Physicians specialty Certificate Examination in Endocrinology and Diabetes, and Nurses will get an indispensable update on best practice and latest developments in the field.

SfE BES 2019
Brighton Centre, Brighton
11-13 NOV

Plan ahead and save the date for SfE BES in 2019. Once again the three-day event will bring together the best in international endocrine research, clinical investigation and best practice.
Images by ENDOCRINOLOGISTS

• Are you a keen photographer?
• Do you take photos with your smartphone?

If so, our new feature ‘Images by endocrinologists’ is yet another reason to read The Endocrinologist.

Send us your best photos (high resolution please), along with either a reason why you like the shot or, if you prefer, simply a title for your photo and your name and institution. Your image should be emailed to: endocrinologist@endocrinology.org. The Editorial Board will choose one or more images to publish inside the back cover of each issue of The Endocrinologist.

Our first image is of the London Aquatics Centre, Queen Elizabeth Olympic Park, London, by Helen Simpson (University College London Hospitals), who is The Endocrinologist’s Associate Editor.

Get snapping!
FLEXIBLE DOsing IN A CONVENIENT CANISTER

The canister accurately dispenses the desired amount of gel (enabling individual dose titration)\(^1\)

- **Tostran\(^{\circledR}\) offers titration in 10mg increments**
  - The usual dose range is 40-80mg per day\(^3\)

- **The first metered dose testosterone canister in the UK.**\(^2\)

- **Quick drying gel**
  - Median drying time is 2.4 mins\(^4\)
  - Patients can shower 2 hours after application\(^1\)

- **Rapidly achieves steady state serum total testosterone concentrations**
  - (Median time 1.13 days)\(^5\)

**RX Tostran\(^{\circledR}\) 2% Testosterone Gel by Brand**

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**References:**
1. Tostran\(^{\circledR}\) Summary of Product Characteristics.
2. AHPI: January 2018.