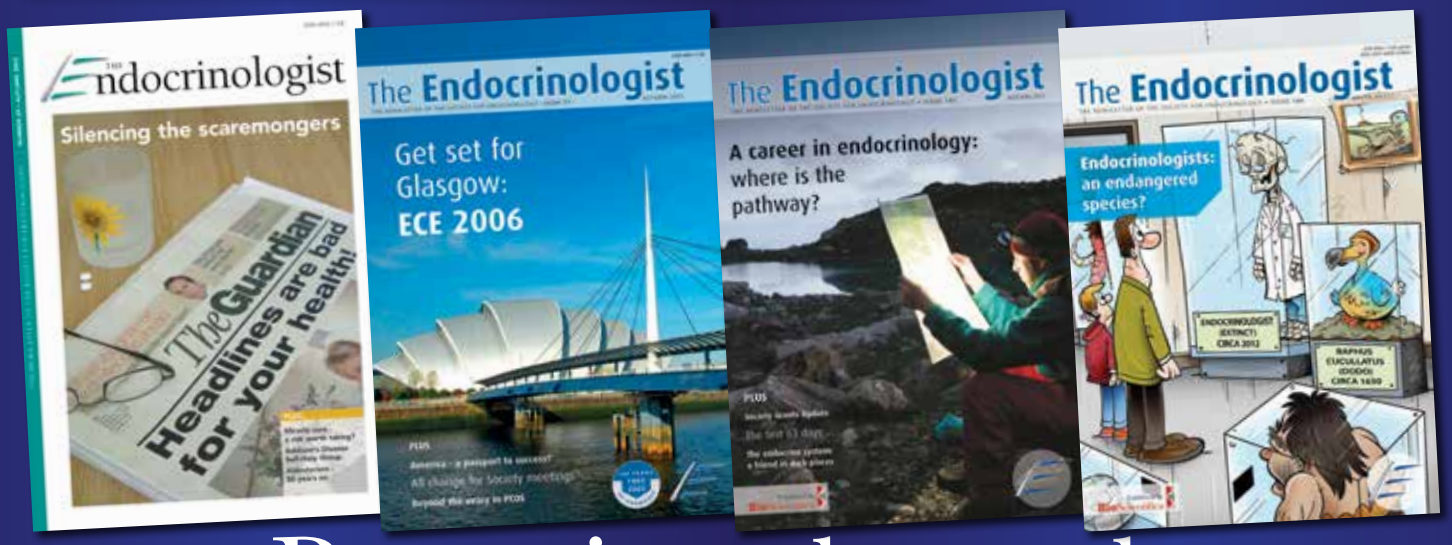
Society for Endocrinology

ISSUE 136 SUMMER 2020
ISSN 0965-1128 (PRINT)
ISSN 2045-6808 (ONLINE)

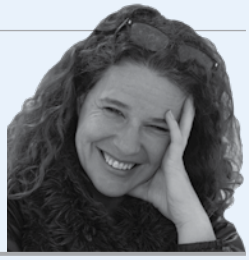
THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY



Browsing through THE ARCHIVES

A word from THE EDITOR...



I'm currently sitting in the garden, fortunate to have some time to pause and draw breath after a tumultuous few months. As life experiences go, I've decided I really don't like living through a pandemic.

For those watching events unfold in the Far East and then Italy, we could see the huge wave that was coronavirus rapidly approaching. By Monday 16 March, we were truly part of the global health emergency. Although advance planning of the NHS left us initially unprepared, NHS hospitals round the country transformed over a number of days, a testament to the dedication and tireless working of our senior leadership teams and all hospital staff, and to the flexibility of the NHS. Early on, the NHS supply chain was unable to deliver PPE and staff were left unprotected. Testing stopped on 12 March and 'ramping up' has been a challenge – research institutions 'repurposed' themselves, working with NHS institutions to provide capacity, and car parks have been 'repurposed' for community testing.

At our hospital, the teams in the ITU and respiratory HDU have borne the brunt, spending many hours in full PPE and seeing the most death. The front line encompasses us all: staff groups such as porters and security teams feature in the roll calls of those who have tragically died. At the time of writing, 35,000 have died in the UK according to government figures, over 60,000 according to those who are analysing the number of excess deaths, many of these being in care homes. The ONS data set shows the highest numbers of deaths in areas of highest socio-economic deprivation and BAME workers.

We are all living with uncertainty, and life has changed for everyone. Hospitals are planning to return to some more usual activity whilst preparing for a second wave. Academics are having to work without their labs, and had grants paused. There is a furious amount of research going on, in particular for drug treatments and for a vaccine. There is a race to publish, a 'pandemic' of unreviewed preprints. Those who are not key workers have been in lockdown, confined to home apart from shopping or exercise, 'Zooming' for team meetings, home-schooling their children. Our teenagers are prowling around at home rather than at Nando's, attending virtual school from their beds. Many of us have been ill. Thankfully, whilst I can describe a cytokine surge, it wasn't so severe I needed hospital. My Amazon pulse oximeter was my best friend for about 10 days.

There is some light, but I can't see an end, more working towards a 'new normal'. There has been an emotional toll for many of us, but we have to have hope. I've loved working on the wards with the 'junior' doctors; in scrubs there are fewer ward-based hierarchies. My friends saw me through scary times. Our post-ITU ward patient is smiling and, importantly, eating! Home is calling him.

Within this Society, there has been a huge amount of work to provide support for our patients and provide COVID-19 resources. We have been working in different ways – remote clinics and virtual meetings – and we have managed to change at pace. Let's not go back. Together, let's continue new ways of thinking and working, and shape our new future.

The Editorial Board of *The Endocrinologist* felt it was inappropriate to expect others to write articles whilst so pressured (contributors – be assured we will return to that issue). Here, instead, is a browse through the archives. We have chosen articles that we thought interesting or which made us smile.

As we all have gone 'virtual' for many areas of life, it seemed apt to read Tony Coll (page 24) musing on acquiring his first iPhone, in prehistoric times. David Oliver (page 14) writes about caring for an elderly population. Tracey Brown (page 7), then as now Director of Sense about Science, wrote in 2003 about managing public debate and the vital role of scientists in communicating with the public – never more relevant. John Newell-Price (page 24) reminds us how we can learn from every patient that we see (something to hold onto during our virtual clinics). And, like a phoenix from the flames, Hotspur writes for us on page 25 – a *purrrfect* summing up of his contributions to endocrinology.

Society news provides an update on many aspects of 'Team Endocrinology's' work during the coronavirus pandemic. Lastly, we say goodbye and thank you to Julie Cragg (page 12), who served the Society tirelessly for over 25 years.

I'd also like to thank Eilidh, Lynsey and the editorial team in the office for all their work producing this issue - no easy task when life and advice changes on a daily basis. they have done a great job. I hope you find this issue enjoyable. My overriding desire is that my family, friends and colleagues should keep well. I wish the same to you and your families: stay safe.

HELEN SIMPSON

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www.endocrinology.org/endocrinologist

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INVIGORATE YOUR TEACHING

Inspire life science students with our awards to help celebrate and support your teaching, and spark a lasting passion for endocrinology in your students.

- Apply for the Society's **Undergraduate Achievement Award** to recognise and promote excellence in the study of endocrinology. Your department could receive £300 per year, for 3 years, to reward outstanding undergraduates for their endocrinology-related studies.
- Celebrate excellence in all forms of teaching and inspire other members with our **Teaching Achievement Award.**

Applications close on 31 July. Find out more at **www.endocrinology.org/careers/invigorate-your-teaching**.

INSPIRE FUTURE ENDOCRINOLOGISTS

Apply for a **Public Engagement Grant** to create learning resources for our website 'You and Your Hormones' or to help school teachers and pupils learn about endocrinology. Funding is available for worksheets, factsheets or quizzes, short videos or podcasts, or anything else you can think of.

Visit **www.endocrinology.org/grants-and-awards/grants/public-engagement-grant** to find out more. Apply by 23 September.

NURTURE EMERGING ENDOCRINE TALENT

Join the Leadership & Development Awards Programme Advisory Group to help support and guide our awardees on their journey to becoming future leaders in endocrinology.

Apply by 30 June. Find out more at **www.endocrinology.org/grants-and-awards/prizes-and-awards/leadership-and-development-awards-programme/advisory-group**.

CELEBRATE EXCELLENT CLINICAL PRACTICE

Our new **Outstanding Clinical Practitioner Award** will recognise a clinical endocrinologist who has made a significant contribution and showed commitment to developing and delivering excellent innovative endocrine care for the benefit of patients.

Nominate yourself, or a colleague, by 31 July. You can learn more at **www.endocrinology.org/grants-and-awards/prizes-and-awards/outstanding-clinical-practitioner-award**.

GRANT AND PRIZE DEADLINES

10 July 2020
MEDAL NOMINATIONS

31 July 2020
UNDERGRADUATE ACHIEVEMENT AWARD

31 July 2020
TEACHING ACHIEVEMENT AWARD

31 July 2020
OUTSTANDING CLINICAL PRACTITIONER AWARD

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

SOCIETY CALENDAR

14 September 2020
RSM: WHAT'S NEW IN ENDOCRINOLOGY AND DIABETES?
London, UK

24–25 September 2020
OXFORD ENDOCRINE MASTERCLASS
Oxford, UK

16–18 November 2020
SfE BES 2020
Harrogate, UK

ENDOCRINE ACADEMY:

14-16 December 2020
CLINICAL UPDATE
Birmingham, UK

14–15 December 2020
ENDOCRINE NURSE UPDATE
Birmingham, UK

15–16 December 2020
CAREER DEVELOPMENT WORKSHOP
Birmingham, UK

www.endocrinology.org/events for full details

HELP MAKE A DIFFERENCE AT YOUR SOCIETY

Apply to join our Council or Committees and help shape the future of endocrinology. The deadline for applications or nominations for is 11 September 2020. There are three vacancies on Council from November: two officers (General Secretary and Programme Secretary) plus an additional Council member.

There are vacancies on the following Committees from 1 January 2021:

- Clinical
- Early Career Steering Group
- Nurse
- Public Engagement
- Corporate Liaison
- Finance
- Programme
- Science

Find out more and apply at **www.endocrinology.org/committee**.

ENDOCRINE CONNECTIONS EDITOR-IN-CHIEF: EXTENDED DEADLINE

This is an exciting opportunity to steer the direction of a fast-growing, open access journal. The deadline to apply has been extended to 1 July 2020.Visit **www.bioscientifica.com/about-us/current-vacancies** for more details.

HOT TOPICS

HT

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

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

For this issue, Hot Topics has changed focus to highlight the most recent (at the time of printing) research into COVID-19. For the latest COVID-19 papers related to endocrinology, we have provided free access to Bioscientifica's content collection at **www.bioscientifica.com/publishing/covid-19-collection**.

The COVID-19 pandemic has changed many things, including the supply of and demand for the latest scientific research. This has placed preprint servers such as *bioRχiv* (**www.biorxiv.org**) and *medRχiv* (**www.medrxiv.org**) in the vanguard, due to their rapid data sharing and open access dissemination.

However, as such studies have not undergone peer review, free public and media access to this unvetted information could lead to health scares and the promotion of unproven treatments.

Although scientific papers published via the 'standard model' have undergone rigorous peer review, they are not exempt from bias or inaccuracy, and it can take many months from completion of a study to publication of the results.

It is clear that rapid data sharing is not only ideally suited to an infectious disease outbreak but essential for developing the strategies needed to end the global COVID-19 pandemic. In the interests of balance, we summarise here the findings of two recent studies: one published in *Science* and one posted in *bioRχiv*.

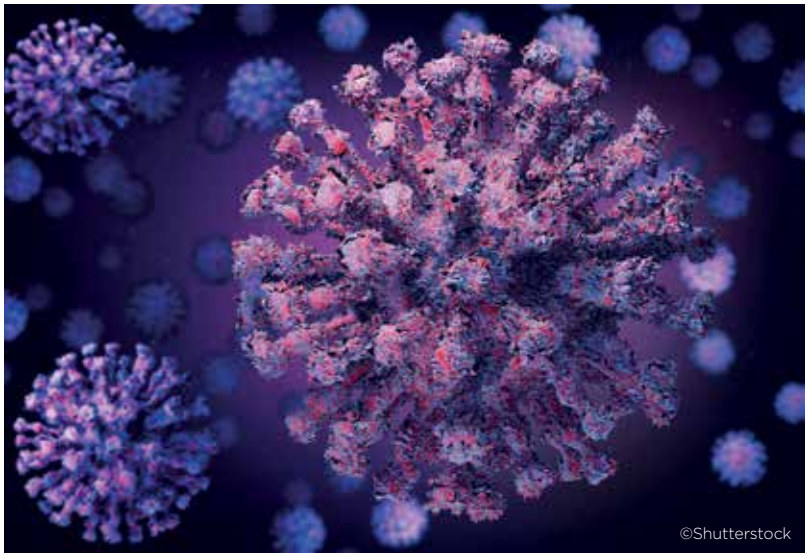
SARS-CoV-2 infection protects against rechallenge in rhesus macaques

Understanding protective immunity to SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) infection is critical for developing vaccine and public health strategies aimed at ending the global COVID-19 pandemic.

One key unanswered question is whether SARS-CoV-2 infection confers protective immunity against re-exposure. The study by Chandrashekar *et al.* (published in *Science*) developed a rhesus macaque model of SARS-CoV-2 infection. Nine adult rhesus macaques were inoculated via intranasal and intratracheal routes with SARS-CoV-2, which resulted in a detectable viral load in bronchoalveolar lavage and nasal swabs and acute interstitial pneumonia. Following initial viral clearance, animals were rechallenged with SARS-CoV-2, which resulted in lower viral loads than those detected with the primary infection.

These promising results in a non-human primate model highlight the potential for protective immunity to SARS-CoV-2. However, the authors caution that SARS-CoV-2 infection in rhesus macaques is less severe than in humans, and that additional research will be required to assess the durability of natural immunity.

Read the full article in *Science* doi:10.1126/science.abc4776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ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques

Vaccines are an essential countermeasure needed to control the global COVID-19 pandemic. The study by van Doremalen *et al.* (posted in *bioRχiv*) shares data demonstrating that the adenovirus-vectored vaccine ChAdOx1 nCoV-19, encoding the spike protein of SARS-CoV-2, is immunogenic in mice and rhesus macaques.

Six rhesus macaques were vaccinated intramuscularly with ChAdOx1 nCoV-19. Virus-specific neutralising antibodies were detectable before challenge in all vaccinated but not control animals. Following SARS-CoV-2 challenge, vaccinated rhesus macaques had a reduced viral load compared with control animals (n=3), and no pneumonia. The authors report that ChAdOx1 nCoV-19 is under investigation in a phase I clinical trial.

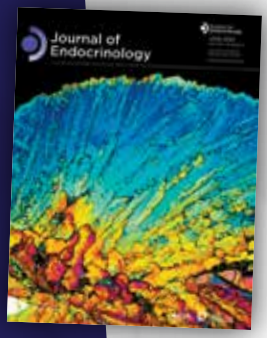
Read the full article in *bioRχiv* doi:10.1101/2020.05.13.093195

Journals are already adapting to expedite publication of COVID-19 studies, while submissions to preprint servers are so numerous that *bioRχiv* now carries a cautionary banner, stating that such studies 'should not be regarded as conclusive, guide clinical practice/health-related behaviour, or be reported in news media as established information'. Whichever way the research is disseminated, early availability of data can help to shape and inform current research, which will be invaluable to the collective research effort.

Society for Endocrinology

www.endocrinology.org/publications

A REMINDER ABOUT THE BENEFITS OF PUBLISHING IN SOCIETY FOR ENDOCRINOLOGY JOURNALS



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NEW! ADULT NHS EMERGENCY STEROID CARD

WRITTEN BY HELEN SIMPSON

The new Adult NHS Emergency Steroid Card has been released in PDF format to be carried by patients with adrenal insufficiency.

CAREFUL DEVELOPMENT

The card's development has been a joint project involving the Royal College of Physicians (RCP) Patient Safety Committee, the NHS England and Improvement (NHSE/I) Patient Safety Group and the Society for Endocrinology.

The wording and information within it have been checked carefully over an extended period of time. Wording is being double checked currently to ensure wording on the reverse incorporates phrases that trigger the response by ambulance services. Clearly the medical advice on the reverse is an initial emergency management guide only.

The QR code on the reverse of the card directs the enquirer to the adrenal crisis page on the Society for Endocrinology website (**www.endocrinology.org/adrenal-crisis**). All relevant details are on that page, which can be updated easily.

FURTHER WORK

Guidance for emergency management of adults with adrenal insufficiency (due to be published soon in *Clinical Medicine*) and an NHS National Patient Safety Alert by NHSE/I (for all sectors of the NHS in England and devolved nations) are also in development, but are on hold during the coronavirus crisis due to workload pressures. Once the alert goes live, healthcare organisations will be time-bound to respond to recommendations.

We hope this will all help place the focus on patient safety issues for our patients with adrenal insufficiency, whether this results from an endocrine condition or exogenous steroid administration causing hypothalamus-pituitary-adrenal axis suppression.

Links to all the relevant guidance on adrenal insufficiency can be found in the Society's COVID-19 web information (**www.endocrinology.org/covid19**).

Other work is underway by a group of rheumatologists and the British Society for Rheumatology to develop patient education in groups on exogenous steroids.

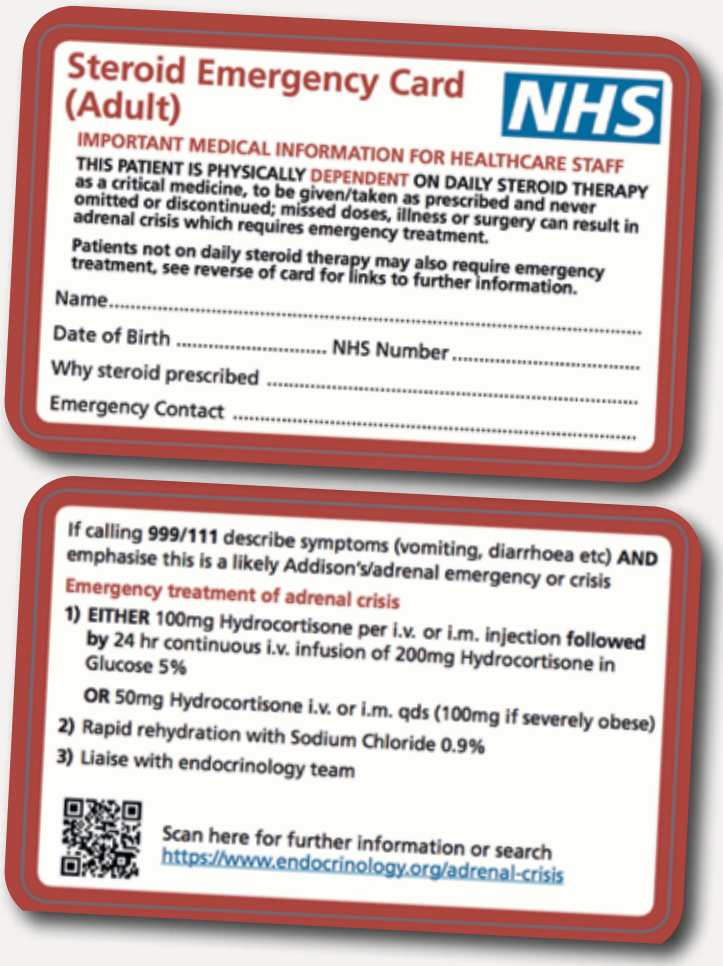
POSITIVE PATIENT RESPONSE

We have been able to release the card in PDF format early, in response to patient safety concerns during the coronavirus crisis. This has had an overwhelmingly positive response from patients, and we are grateful to the Addison's Disease Self-Help Group , CAH Support Group and The Pituitary Foundation for their support in sharing the card with their members during the pandemic.

Indeed, some patients have used the image of the card, with emergency contact details, as a lock-screen on their phone, whilst others have produced credit card-sized versions themselves and laminated them to carry them around. This has been lovely to see, and I think the card will make a real difference to patient safety.

NEXT STEPS

The RCP and NHSE/I are now discussing how we distribute the card in tandem with the National Patient Safety Alert, as well as other practical matters such as ensuring GP and community pharmacy teams have any



educational resources they may need. The card will be available to order through the usual NHS procurement processes, in addition to the downloadable PDF version.

We also need to form links with our paediatric colleagues, to ensure messages are not mixed: particularly for our adolescent patients, and BSPED is taking this forward. And, of course, also all of us in the Society will be key in educating our wider teams in our own organisations.

A SUCCESSFUL COLLABORATION

So, after a long time, the work started by Wiebke Arlt and John Wass is coming to fruition. We would not have managed this without John Dean (Clinical Director for Quality Improvement and Patient Safety at the RCP) and Julie Windsor (Patient Safety Group NHSE/I). It has been a huge team effort across multiple organisations: the Society for Endocrinology, the RCP, NHSE/I, the British National Formulary and the Royal Pharmaceutical Society, to name a few. I have learnt a huge amount about working with others across multiple national bodies.

Light has definitely been spotted at the end of the tunnel.

HELEN SIMPSON
on behalf of the RCP Patient Safety Committee and Society for Endocrinology Clinical Committee

SOWING THE SEEDS OF SENSE

WRITTEN BY TRACEY BROWN

FIRST PUBLISHED IN ISSUE 69 (2003)

When endocrinology hits the headlines, it isn't always for the reasons the researchers had in mind. The trust, Sense About Science, promotes evidence-based public debate about science and risk. Here, the trust's Director, Tracey Brown, talks about managing public debate.

A quick rummage through recent fragmented memories of popular exposure to endocrinology produces a nonsensical sensationalist stream: HRT is a risk not worth the benefit, it apparently causes cancer; growth hormone – there was a problem with weight lifters using it, it comes from dead bodies, it also causes cancer; the hormones they put in meat make you immune to antibiotics; in the USA young girls develop breasts earlier because of the hormones in food (or is it that they get facial hair?); genetically modified food can make men sterile…

No doubt you can remember an even longer list of popular claims. As regards public clarity about scientific evidence, endocrinology seems particularly scare-prone, because of its intimate connection with social behaviour, human health, current therapies and environmental exposures. Often, scientists' results are released into wider debates that are already polarised or political. For example, hormone therapies have their advocates and detractors, and claims about 'gender bending' effects are *de rigueur* for environmental campaigners against agricultural chemicals, anti-GM groups, and some alternative health practitioners.

According to Robin Lovell-Badge, developmental geneticist at the MRC National Institute for Medical Research, endocrinology's inherent complexity doesn't help. For instance, when considering endocrine disruption, 'There are all sorts of variables in the way a chemical is handled both in the environment and in an organism. Results in this field rely on data that are difficult to collect in a uniform way, and consequently there are rarely 'clean' answers.' Indeed, the WHO's recent report on endocrine disruptors concluded that the publicity accorded to the area was not supported by convincing experimental data.

While this may help prioritise future research, the immediate challenge is how to achieve a measured discussion about the available evidence. In this regard, I suspect that endocrinologists, like other scientists, need to become more confrontational.

No doubt confrontation sounds at odds with our self-effacing, 'dialogue' focused times. But, before dismissing it, consider this paradox: despite the proliferation of 'science communication' initiatives, the rebranding of every aspect of society's interface with science as a 'science and society' project, and a general anxiety about ensuring 'stakeholder consultation', have relations ever felt worse between the scientific community and society at large? Have the media ever been so controlling of how scientific claims are communicated? Has there ever been such scepticism about the role of science in social progress?

Most modern scientists are pleased to have distanced themselves from earlier methods of confronting public scares – which often took the form of a condescending dismissal! However, the adoption of alternative, effective ways of confronting distortions has not been straightforward. Scientists' increased sensitivity to potential opposition seems also to have made them reticent when problems arise. More significantly, the scientific world has never before had to compete with so many health groups, environmental campaigns, campaigning journalists and new age therapy promoters, among others, each vying to comment on findings.

At Sense About Science, we encourage scientists to take on the challenges of the broader implications of their work at two levels. The first is straightforward – to think about how claims are likely to be presented. Good advice is readily available. The Science Media Centre, established last year to respond when science hits the headlines, helps anticipate the media reaction to results. Professional and learned societies also provide a (currently under-utilised) resource. They should at least be informed about work entering the public domain. The scope for generating public confusion is greatest when unprepared contacts are asked for their reactions. The Society for Endocrinology, according to External Relations Officer Tom Parkhill, still learns late in the day about research news, 'most often because the press ring up asking for a response.'

The second level is to think more strategically about relationships with groups who have a role in how research results are received and understood, and to confront people directly over mistakes and disagreements. Active relationships can remove the scope for misunderstanding, and even for mischief. When we know people, we feel more compelled to confront them directly with disagreements rather than to project them publicly straightaway.

Public scares about scientific matters are usually generated by active players, which include a wide range of institutions that shape public opinion, beyond the journalists on whom we tend to focus. Commentators on recent public scares have often been able to generate alternative interpretations of results in a relatively unimpeded way, with little insistence on distinctions between evidence and conjecture. When I speak to organisations with concerns about conservation, health risks and pollution, they have usually neither sought nor received contact with the scientists whose research they are reacting to, but have been dependent on news releases and discrete discussions among themselves.

Where scientists make direct contact with other commentators, it improves the public debate. Organisations that shape public opinion need to be treated in different ways. A few campaigns' credibility is dependent on undermining scientific evidence *per se*. In most cases, however, being prepared to confront the sources of misinterpretation can set up useful relationships. Some scientists involved in research using animals and stem cells are directly in touch with interested medical charities, and we can see the benefits of this in recent discussions about the need for such work. At Sense About Science, we have created opportunities – some more challenging than others – for scientists to discuss evidence with people from conservation groups, aid NGOs, medical bodies and writers of parenting literature, among others.

Seeking direct, active engagement with the people who make the arguments influential may be less appealing than the vaguer consultations that often pass for 'dialogue', but it offers the only real prospect of being effective in reducing public scares. Those scientists who have been willing to confront significantly misleading claims are often rewarded with a better understanding of what different commentators represent, and the source of their reactions and anxieties. That understanding puts scientists more firmly in a position to swing the balance of public discussion away from scares and in favour of evidence.

TRACEY BROWN
Director, Sense About Science

For more information see ***www.senseaboutscience.org*** *or email* ***tbrown@senseaboutscience.org***.

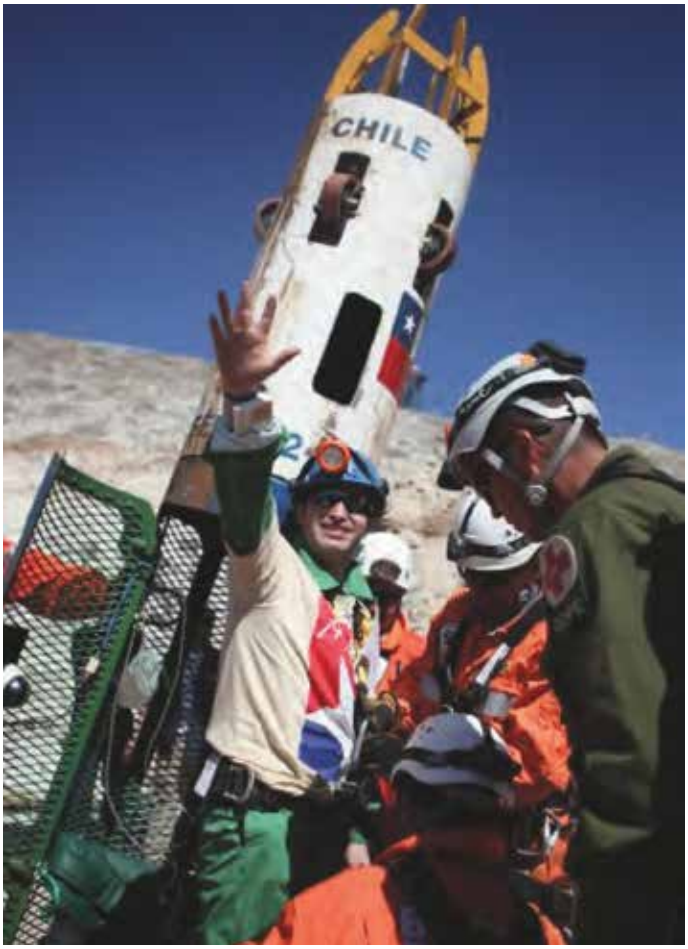
THE ENDOCRINE SYSTEM: A FRIEND IN DARK PLACES?

WRITTEN BY FREDERICK VONBERG

FIRST PUBLISHED IN ISSUE 101 (2011)

For 69 days, 33 men were trapped more than 2000 feet underground in a collapsed mine near Copiapó, Chile. A huge and successful rescue effort was launched, and both the miners and rescuers were rightly praised for their tenacity and endurance. I would like, however, to consider the contribution of an unsung hero: the endocrine system.

Being trapped in a hot, dark, confined space with very limited supplies is an extremely stressful situation, both physiologically and psychologically. There are various endocrine mechanisms that respond to stress in an attempt to limit the damage. One of the best characterised of these is the release of cortisol. Stimuli such as trauma, decreased oxygen, pain, fright and starvation, all of which were features of the miners' experience at various points, lead to an increase in the secretion of cortisol from the adrenal cortex. By stimulating gluconeogenesis in the liver, catabolism of triacylglycerol in adipose tissue, and protein catabolism, the cortisol helps to maximise energy supply to the body's cells and ensure that fuel for the brain is prioritised.



Cortisol was not the only hormone active in the mine. The temperature was high (30°C) and the water supply was limited. The miners' restricted fluid intake would have led to the release of anti-diuretic hormone (ADH) from the posterior pituitary and aldosterone from the adrenals. Both hormones prevent water loss and, in addition, ADH induces vasoconstriction to maintain adequate tissue perfusion despite a decreased circulating volume.

However, the endocrine response may not have been entirely beneficial. Chronically elevated cortisol, combined with extended inactivity in cramped conditions, would result in muscle atrophy and osteoporosis: exercise advice from NASA was sought.

Cortisol's suppressive effect on the immune system was also a risk, as conditions were ideal for the spread of infection. One of the men suffered pneumonia, several had severe dental problems and many suffered skin complaints. It is conceivable that elevated cortisol made these infections worse, as has been demonstrated in people with depression, which is also characterised by high cortisol.

The most dangerous aspect related to elevated cortisol for the miners was, however, the effects it can have on mood. The morale of the miners was apparently remarkable, but chronically elevated cortisol can lead to depression and irritability. Given the very real importance of maintaining good spirits, the effects on mood may have been the most serious endocrine-mediated threat to the miners.

As well as being a very stressful place, the collapsed mine was also very dark. The body requires energy from the UV component of sunlight to convert cholesterol into vitamin D. Vitamin D is then converted into active 1,25-dihydroxycholecalciferol which maintains calcium and phosphate levels. In the mine there was no sunlight at all – to receive a dose of UV radiation equivalent to 1 minute of sunlight, the miners would have had to sit under a fluorescent lamp for 8 hours. Vitamin D deficiency, in turn, increased the risk of osteomalacia.

Low calcium can have other, potentially lethal, effects too – including cell hyperexcitability and muscle spasm. Luckily, the endocrine system can counter this by releasing parathyroid hormone, returning serum calcium back to acceptable levels. This solution, however, acts as both friend and foe: the calcium is derived from enhanced bone osteoclastic activity, compounding the bone weakening effect of elevated cortisol and vitamin D deficiency.

So, in the end, were the miners helped or hindered by their endocrine systems? This essay has tried to show how the miners would almost certainly have died were it not for their endocrine systems. It is also true that some endocrinological effects were not beneficial and may even have endangered the miners. Is this surprising? While the fantastically complex endocrine system has evolved in response to various environmental pressures, it is unlikely that these included subterranean incarceration! We should also bear in mind what Shakespeare's Othello would have called 'the ocular proof': despite the endocrine system's shortcomings, all the miners came out alive and remarkably healthy. Thus, as the Chilean government rallied to save the miners, their co-ordinated efforts were being mirrored on a much smaller, but equally important, scale 2000 feet below them, in the endocrine system of each miner.

FREDERICK VONBERG

CONGENITAL DISORDERS OF PITUITARY DEVELOPMENT: MOLECULAR GENETICS AND MANAGEMENT

WRITTEN BY MEHUL DATTANI

FIRST PUBLISHED IN ISSUE 116 (2015)

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

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

THE MOLECULAR BASIS OF CH

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

POU1F1 AND *PROP1* MUTATIONS

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

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

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

A further feature of the phenotype is the transient enlargement of the pituitary gland, when the possibility of a tumour may be raised. However, the size of the pituitary can wax and wane before its eventual involution.

Generally, the phenotype of patients with *PROP1* mutations is that of GH, TSH, prolactin, ACTH and gonadotrophin deficiencies, with a small anterior pituitary and a normally placed posterior pituitary. To date, PROP1 deficiency seems to be the commonest genetic cause of hypopituitarism, accounting for 50–100% of familial cases, although only around 10% of sporadic cases are due to *PROP1* mutations.

HESX1 MUTATIONS

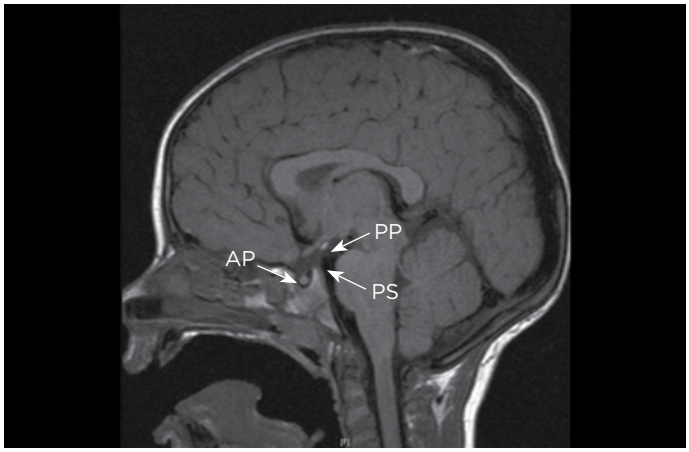
In 1998, the story became more complex with the identification of mutations in a transcriptional repressor gene called *HESX1*, initially in association with SOD, but later with GH deficiency and combined pituitary hormone deficiencies (CPHD) without midline or eye defects being added to the phenotypic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

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

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

LHX3 AND *LHX4* MUTATIONS

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



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

pituitary may be small or occasionally enlarged, with the appearance of a microadenoma. The posterior pituitary is always eutopic, however.

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

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

OTHER MUTATIONS

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

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

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

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

THE NEXT STEPS

Much has been achieved in terms of our understanding of hypothalamo-pituitary development and the aetiology of CH. On the other hand, we can only identify a genetic basis in around 15% of CH cases, suggesting that other genes remain to be identified. The use of whole exome and potentially whole genome sequencing may lead to an improved understanding of the condition.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In particular, it is likely that, as observed with Kallmann syndrome, mutations in more than one gene may lead to the variable penetrance, and hence phenotypic expressivity, of hypopituitarism and SOD. Many other questions will need a more basic approach, for example the aetiology of the pituitary masses associated with *PROP1* and *SOX2* mutations. Close collaboration between basic scientists and clinicians will be required to further the field.

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

CLINICAL RELEVANCE OF MOLECULAR GENETICS IN CH MANAGEMENT

Understanding the molecular basis of CH can actually have an impact on its clinical management. For example, the identification of *POU1F1* mutations would rule out the possibility of ACTH and gonadotrophin deficiencies, whereas the presence of *PROP1* mutations might alert one to the probability of evolving ACTH deficiency, and encourage a more relaxed approach to the presence of a pituitary mass.

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

MEHUL DATTANI
Currently Head of Paediatric Endocrinology at Great Ormond Street Hospital for Children (GOSH), University College London Hospitals (UCLH) and Institute of Child Health (ICH), London

Farewell Julie!
THE END OF AN ERA

We recently bid a sad farewell to one of our longest standing employees, Julie Cragg, who has now retired. Julie worked for the Society for over 25 years in a number of roles, and has contributed enormously to its success.

She saw the Society grow and develop over the years, and her experience and witty personality will be sorely missed by all. We wish her all the best in her retirement and would like to say a final, huge, thank you for all her hard work.

In this interview, Julie shares some of her experiences over 25 years at our Society.

HOW DID YOU START WORKING AT THE SOCIETY?

Many years ago, I worked as a medical secretary for an orthopaedic consultant, followed by some time spent at home as a full-time mum. I first started working for the Society as a temp on a 2-week assignment. Even as a temp, I realised that working for the Society was something very special, so I was over the moon when I received a phone call asking if I would be interested in a permanent role. So, 25 years ago, I started as an admin assistant working closely with Janet Crompton and Amanda Sherwood, with Chief Executive, Sue Thorn.

WHAT DID YOU ENJOY MOST?

It has to be helping the inspiring people who devote themselves to looking after patients and who research endocrine conditions. When asked, as a small child, what I would like to do when I grew up, I always said I wanted to be a doctor. Sadly, that didn't happen for several reasons, so my work ethic has always been to do my best to support those on the front line. Simply put, the Society is like my second family. I have worked with many members and made so many friends over the years.

HOW HAS THE SOCIETY CHANGED OVER THE LAST 25 YEARS?

Well, suffice to say, it has changed a fair bit! When I first started, there were only seven of us; now our organisation has over 80 employees. About a year after I started, we were able to gain access to the internet via one computer in the office, which belonged to the Chief Executive's PA. You had to commandeer her computer and use a dial-up modem, which sang you a happy tune followed by a series of buzzes, whirrs and general electronic babble.

It has never ceased to amaze me how far we have come since those times, when your only way of communicating was by post, fax or phone, and communication with far-flung places took days.

Abstracts for the Society's meetings were received as hard copy by post, accompanied by five photocopies. The entire abstract selection process and author notification process was again handled by post, which meant laying out 500 different piles of abstracts all over the office floor. Luckily, there was just room to do this – provided no-one wanted to walk across the office… Now it happens at the touch of a button.

The major growth in office staff happened when Bioscientifica was established, necessitating three different offices over the last 25 years.

WHAT DO YOU HOPE THE FUTURE HOLDS FOR THE SOCIETY?

I hope that the Society continues to thrive and to expand its activities. I hope that Bioscientifica's business plans come to fruition, because that is where the Society derives its Gift Aid that financially supports all the activities for members, patient groups and the general public.

WHAT HAS BEEN YOUR ROLE AT THE SOCIETY?

I have held several roles over the years but, 3 years ago, I became Society Governance Manager, after the Society Engagement Team was restructured. That role included many things but, essentially, I focused on ensuring that we didn't contravene the Articles of Association or Byelaws, as well as managing the membership of 11 committees.

I was directly responsible for three of those committees – the Council of Management, the Officers' Sub-Committee and the Nominations Committee – and for the AGM. On these, I worked very closely with Ian Russell (Chief Executive) and with Laura Udakis (Director of Membership Engagement). I was also involved in managing the Society's prizes, awards and medals.

Before that, I was Society Services Manager. As well as some of the above, this entailed managing the Society's grant and membership processes.

WHAT WILL YOU MISS THE MOST?

I will miss everyone very much. I will miss the camaraderie of being able to go to Society events, to meet and talk with members. I will miss my colleagues in the office, particularly those in the Society Engagement Team. On the plus side, I will have time to garden all day long, every day, if I want to, and am so lucky to have that space, particularly at the moment (at the time of this interview we are all in lockdown). I sincerely hope that things will improve soon and I will be able to go and do the things that I had planned.

WHAT ADVICE WOULD YOU GIVE TO YOLANDA, THE 'NEW YOU'?

I hope Yolanda enjoys the role as much as I have done. Never forget that everything that members do for the Society is on top of their extremely demanding 'day jobs'. In all your dealings with members, put yourself in their shoes, and always think about what would make their lives easier when planning your actions and communications.

AND FINALLY...

On a personal note, I have grown as a person and done some really amazing things in my time, which I could never have imagined doing. And this, from someone who never really knew what she wanted to do, is pretty good.

I wish you all and the Society the very best for the future. I look forward to keeping in touch via my Honorary Membership, which Council very kindly bestowed upon me, so I can come to the SfE BES conference if I want to. It has been a great honour: au revoir!

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

WRITTEN BY DAVID OLIVER

FIRST PUBLISHED IN ISSUE 116 (2015)

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

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

WHY WE SHOULD CELEBRATE

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

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

IDENTIFYING NEEDS OF OLDER PEOPLE

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

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

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

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

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

CHALLENGES FOR CHANGE

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

But we need radically to change our priorities and approach away from one designed for a population who died far younger or to deal with single

conditions or episodic disease. Instead we need a focus on:

- prevention across the life course
- ensuring that when older people start to become frail or unwell we maintain their independence, connections and ability to remain at home
- more continuity and 'person-centred co-ordinated care' for people living with frailty, dementia and multiple complex co-morbidities and based around them as individuals rather than single disease entities
- support for carers (there are around six million in the UK, many of whom are older people themselves)
- better collaboration and integrated working between hospital, primary and community care and social care (including the need for far more responsive rehab and support services outside hospital or better healthcare for nursing home residents).

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

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

DAVID OLIVER
At the time of writing David Oliver was President of the British Geriatrics Society and Senior Visiting Fellow at The King's Fund

FURTHER READING

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MOVING MUSCLE MOLECULES: THE BENEFICIAL EFFECTS OF EXERCISE IN SKELETAL MUSCLE

WRITTEN BY ANNA KROOK

FIRST PUBLISHED IN ISSUE 120 (2016)

Increased time spent exercising is positively linked to a reduction in all-cause mortality.[1,2] Furthermore, lack of physical activity is a significant risk factor for development of many prevalent non-communicable diseases, ranging from various forms of cancer, type 2 diabetes, cardiovascular disease and hypertension to Alzheimer's disease and depression.

Physical activity is linked to increased number of healthy years. It has been proposed that when it comes to reducing the risk of virtually all chronic diseases simultaneously, there is probably no single intervention with a higher therapeutic potential than physical exercise, and this with few or no adverse side effects.[3]

Exercise results in a plethora of changes in several different organs, including effects on the cardiovascular system, muscle and bone. This review focuses on exercise-mediated effects in skeletal muscle.

MUSCULAR ADAPTATION

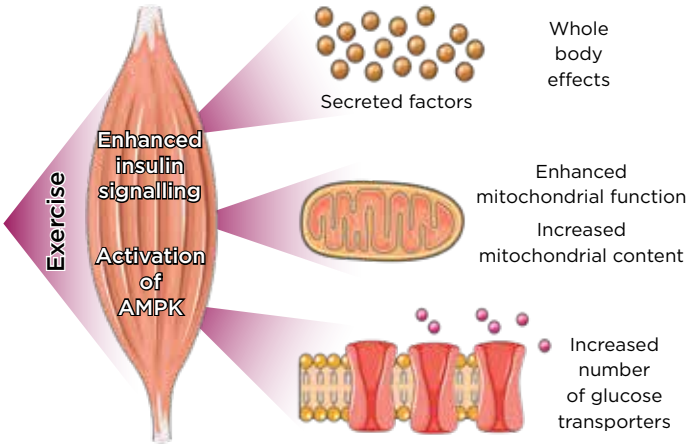
Skeletal muscle is a highly plastic and adaptive organ. Muscle contraction is a physiological stress to the muscle, which responds by remodelling gene expression to adapt to increased functional demands. The well-trained muscle is characterised by changes in contractile proteins and function, and enhanced mitochondrial function and content.[4]

The trained skeletal muscle is stronger, has higher endurance, and is able to more efficiently utilise and switch between different nutrient sources. While exercise-induced muscle growth is perhaps a more intuitively appreciated response to muscle use, it is the exercise-mediated changes in the capacity for substrate metabolism and insulin sensitivity that probably have the more important implications for overall health.

PHYSICAL ACTIVITY AND DIABETES

The positive effects of physical activity are well documented for type 2 diabetes.[5] Skeletal muscle is an insulin-responsive organ and the primary site for post-prandial glucose disposal. Skeletal muscle insulin resistance, leading to a reduction in insulin-stimulated glucose disposal, is often an early defect contributing to the development of type 2 diabetes.

In response to a rise in blood glucose, insulin is rapidly released from the pancreas, leading to increased glucose uptake, primarily into skeletal muscle and adipose tissue. Muscle contraction also results in a similar and rapid increase in glucose uptake into the working muscle. Contraction-activated glucose uptake does not utilise the same molecular pathways as



Some of the changes noted in skeletal muscle in response to exercise.
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insulin, and occurs also in the absence of insulin, making this pathway an attractive target for bypassing insulin resistance.

INSULIN-INDEPENDENT GLUCOSE UPTAKE

Uncovering the molecular mechanisms that mediate this insulin-independent glucose uptake has been the focus of much recent research, and has led to the identification of a number of different pathways, with the most emphasis being placed on activation of AMP-dependent protein kinase (AMPK). As the muscle performs work and consumes ATP, the ratio of AMP to ATP increases in the muscle, which leads to activation of AMPK. Activated AMPK inhibits energy-consuming biosynthetic and anabolic pathways, while increasing glucose uptake and promoting β-oxidation of fatty acids within the mitochondria, thus serving to restore cellular energy balance. Targeted activation of the contraction-mediated pathway to glucose uptake is a potential strategy to promote glucose uptake into insulin-resistant muscle.

In response to training, i.e. several bouts of repeated exercise, skeletal muscle adapts to increase the number of glucose transporters and number of mitochondria, thus facilitating both the uptake of glucose and the rapid generation of ATP, to meet increased demands.

ADDITIONAL PATHWAYS

Activation of AMPK mediates some of the muscle remodelling noted in response to exercise training. However, several other molecular pathways are known to play important roles in both the acute and chronic response to exercise. These include (amongst others) contraction-mediated activation of stress kinases, changes in redox balance and reactive oxygen species, and pathways responding to changes in intracellular Ca^{2+}.

A recent analysis of the human exercise-activated muscle phosphoproteome has provided a more unbiased snapshot of which proteins are phosphorylated in response to muscle work,[6] and further analysis of some of the molecules identified should provide an insight into previously unknown exercise-activated pathways.

HOW MUCH EXERCISE IS EFFECTIVE?

While training leads to persistent effects in skeletal muscle, even one single bout of exercise leads to an enhancement in skeletal muscle insulin sensitivity. This phenomenon is probably most sharply appreciated by people with insulin-dependent (type 1) diabetes, who need to reduce their insulin doses after performing exercise. The enhanced insulin sensitivity persists for several hours post-exercise and, although the precise mechanisms that mediate this effect are less well explored, there is evidence that activation of AMPK may also play an important role in this effect of exercise.

EFFECTS ON OTHER ORGANS

In addition to local changes within the exercising muscle itself, the contracting muscle generates factors secreted into the circulation with potential to alter the metabolism and function of other organs. For example, brain-derived neurotrophic factor increases in skeletal muscle in response to exercise[7] and has been implicated as a potent mediator of exercise-dependent enhancements in learning and memory. Recent evidence also indicates that exercise training alters muscle enzymes that directly modulate circulating levels of kynurenine metabolites to protect from stress-induced depression.[8]

Numerous other factors have been described which are released from muscle in response to exercise, ranging from hormones to cytokines to microRNAs. However, the nature of the precise signals produced, and the subsequent target tissues, remain to be fully explored.

FACILITATING THE BENEFITS OF EXERCISE

While unravelling the molecular machinery that remodels muscle in a way to promote overall health may lead to new therapeutic insights, a separate challenge is encouraging better exercise habits in the population. Given that lack of time is the most common explanation for failure to exercise, identification of the most beneficial and time-efficient form of exercise should be valuable.

Clearly, not all people respond in the same way, or with the same magnitude, to any given exercise intervention, and a proportion of people have disappointing clinical outcomes even when the exercise appears to have been adequately performed.[9] Careful analysis of the exercise response at a molecular level in high as well as low responders will give insights into the relative roles of different exercise-activated molecular pathways, and may be able to inform personalised exercise intervention programmes to ensure maximum benefits.

It is likely that exercise low-responders are over-represented amongst people developing diseases linked to lack of exercise. Since this population is likely to also include people who are less able to exercise, finding effective pharmaceutical exercise mimetics will be helpful, although to date this has been challenging. In the meantime, identifying the most effective type of training programme for each person should improve the efficacy of exercise interventions, and lead to important public health benefits.

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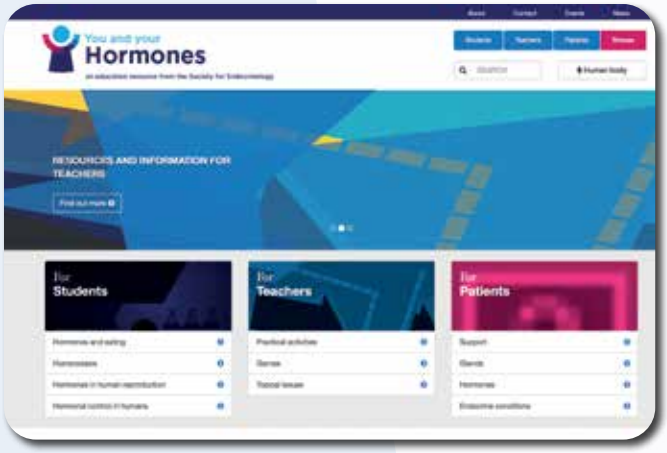

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BEYOND THE OVARY: STEROIDS AND PCOS

WRITTEN BY WIEBKE ARLT

FIRST PUBLISHED IN ISSUE 77 (2005)

Wiebke Arlt takes a fresh look at a common endocrine disorder.

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, affecting 5–15% of the female population. PCOS has a huge and possibly insufficiently acknowledged impact on the nation's health, as an early marker disease for cardiovascular risk.

At least half the women with PCOS are insulin-resistant and at an increased risk of developing the metabolic syndrome, including obesity, hyperlipidaemia, high blood pressure and type 2 diabetes. Furthermore, chronic anovulation due to PCOS is the most frequent cause of female infertility. Related treatment consumes the largest part of fertility treatment costs in the UK. Pregnancy in PCOS, once achieved, is not straightforward either, with a tenfold-increased risk of gestational diabetes and pregnancy-related hypertension.

PCOS was first described in 1935 by Stein and Leventhal, who found bilateral polycystic ovaries in women with amenorrhoea at autopsy. Nowadays, luckily, we can catch these women earlier. Many of them initially present with mild obesity and oligomenorrhoea and hirsutism. Motivating them to comply with treatment may help to avoid the detrimental consequences of full-blown metabolic syndrome in later life. It is often useful to realise that these women may be genetically advantaged, as they would be the most likely to survive and even reproduce in times of extreme food restriction like poverty, hunger and war.

Though it is obvious to doctors that the term 'syndrome' implies that the underlying cause of disease is unclear, patients tend to interpret 'polycystic ovary syndrome' quite literally and anxiously look for treatment options to heal their ovaries. It is often difficult to explain the complexity of PCOS, that it is probably genetically determined and that it affects the whole endocrine–metabolic set-up. Patients therefore often wonder why dieting should get rid of cysts in their ovaries.

Most confusingly, the ultrasound appearance of polycystic ovaries is not necessarily a precondition for diagnosis. Two of the following are required for diagnosis of PCOS, according to the Rotterdam 2003 PCOS Consensus Workshop: (a) oligo- or amenorrhoea, (b) clinical or biochemical signs of hyperandrogenaemia, (c) polycystic appearance of ovaries at ultrasound (as defined by more than 12 cysts with a diameter of 2–9 mm).

Furthermore, polycystic ovaries are not necessarily indicative of PCOS. The work of Steve Franks and others tells us that polycystic ovaries at ultrasound are seen in a considerable number of women, without concurrent clinical evidence of the syndrome. Whether polycystic ovaries without PCOS represent a preclinical stage of the disease or an unrelated entity is a matter for debate.

Importantly, endocrine researchers, like patients, tend to restrict their view of PCOS to the ovary, especially when considering the origin of hyperandrogenaemia, one of the syndrome's main clinical features. *In vitro* studies have shown excess androgen production by theca cells isolated from ovaries in PCOS. This includes increased activity of 5α-reductase, resulting in increased conversion of testosterone to dihydrotestosterone (DHT), which binds the androgen receptor with tenfold higher affinity than testosterone.

However, whilst this seems to imply that the problem lies primarily in the ovary, earlier studies by Paul Stewart and colleagues provided indirect evidence that 5α-reductase activity may generally be enhanced in PCOS. They found that patients had increased urinary baseline excretion of 5α-reduced androgen and glucocorticoid metabolites. We have now revisited this concept using a dehydroepiandrosterone (DHEA) challenge test.

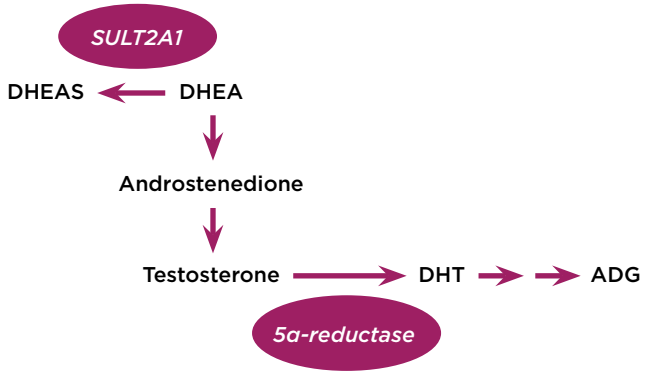
DHEA is a crucial precursor of human androgen synthesis, and we have previously shown that oral administration of DHEA leads to its efficient conversion towards androgens in women. Comparing women with PCOS and healthy controls, the oral DHEA challenge, preceded by dexamethasone suppression, was a tool to detect differences in downstream androgen generation.

While levels of androstenedione and testosterone following DHEA administration did not differ between groups, women with PCOS showed significantly higher generation of DHT and the DHT metabolite ADG, i.e. upregulation of all androgens downstream of 5α-reductase (see Figure).

This was further supported by urinary steroid excretion analysis, which revealed a significantly increased excretion of 5α-reduced androgen, glucocorticoid and mineralocorticoid metabolites following DHEA administration. A general increase in 5α-reductase activity will inevitably lead to enhanced androgen activation by conversion of testosterone to DHT in peripheral target cells of androgen action. This clearly highlights the importance of liver and other target tissues in a novel, 'beyond the ovary' perspective on hyperandrogenaemia in PCOS.

Our recent study on the interconversion of DHEA and its sulphate ester, DHEA sulphate (DHEAS), may have exposed another novel perspective.

Only desulphated DHEA is biologically active and can be converted towards androgens. It has previously been assumed that DHEA and DHEAS interconvert freely and continuously, DHEAS being activated to DHEA by steroid sulphatase, and DHEA inactivated to DHEAS by DHEA sulphotransferase (SULT2A1). So DHEAS is usually seen as a circulating storage pool for continuous DHEA regeneration.



Downstream conversion of DHEA towards androgens, highlighting the two enzymes recently implicated in PCOS-related hyperandrogenaemia: 5α-reductase (activating testosterone to DHT) and SULT2A1 (DHEA sulphotransferase, inactivating DHEA to DHEAS).

However, while DHEA administration yields rapid generation of active androgens, we showed that administration of DHEAS did not lead to an increase in either DHEA or downstream androgens. This suggests that SULT2A1 activity, i.e. the inactivation of DHEA to DHEAS, appears to be the rate-limiting step regulating the DHEA–DHEAS equilibrium, determining DHEA bioavailability. These *in vivo* findings were supported by concurrent *in vitro* experiments, demonstrating ample generation of DHEAS from DHEA in cultured liver cells, but a complete lack of conversion of DHEAS to DHEA.

Serum DHEAS measurements are generally used as an estimate of adrenal androgen generation. However, from our recent findings, it seems highly likely that serum DHEAS may not appropriately reflect corresponding levels of desulphated, biologically active DHEA. Serum DHEA and DHEAS may be concordant in the physiological situation, but will be discordant in pathological conditions, in particular if SULT2A1 activity is impaired.

Hyperandrogenaemia of adrenal origin is usually excluded by measurement of serum DHEAS. A woman with normal DHEAS and increased androstenedione levels is generally considered to have hyperandrogenaemia of primarily ovarian origin. Most women with PCOS show this pattern, so seeming to justify the concentration of research into PCOS-related hyperandrogenaemia on mechanisms underlying ovarian androgen hypersecretion.

However, although serum DHEAS is normal, it may be that biologically active DHEA is pathologically increased, resulting in increased androstenedione through efficient downstream conversion of DHEA. Increased DHEA levels with concurrently low–normal DHEAS levels would suggest impairment of SULT2A1 activity. Preliminary findings in a large PCOS cohort, which we presented at BES 2005, revealed that a significant proportion of women with PCOS showed exactly that pattern.

One could argue that increased DHEA levels may result from enhanced ovarian CYP17 activity, the enzyme responsible for DHEA biosynthesis. However, we have shown that dexamethasone administration yields a similar and near complete suppression of serum DHEA in both healthy controls and women with PCOS, suggesting a primarily adrenal origin of circulating DHEA in both groups. This leaves SULT2A1 impairment as a potential novel mechanism underlying hyperandrogenaemia in PCOS.

These two mechanisms, enhanced 5α-reductase activity and putatively impaired SULT2A1 activity, illustrate the importance of steroidogenesis in understanding the pathophysiology of PCOS. A systemic view, rather than an ovarian spotlight, is likely to generate further insights into this fascinating disease.

WIEBKE ARLT

THYROID REGENERATIVE THERAPY: NEW INSIGHTS

WRITTEN BY ANTHONY N HOLLENBERG

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

FIRST PUBLISHED IN ISSUE 125 (2017)

FOLLICULAR CELL DEVELOPMENT

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

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

In order to induce thyroid development from murine ESCs, investigators initially used a variety of techniques, including generating ESCs that possess a labelled thyrotrophin (TSH) receptor, so that cells poised to

differentiate appropriately could be identified.[1] While such techniques produced follicular-like structures in culture, it was not clear if they had the capacity to produce thyroid hormones.

CREATING FUNCTIONAL FOLLICLES

The first major breakthrough in this area was made by the laboratory of Sabine Costagliola, who co-expressed Nkx2-1 and Pax8 at a very early stage of mouse ESC development.[2] By then adding TSH and providing a 3D culture system, these ESCs were able to develop into follicular structures that expressed thyroglobulin and also had the ability to take up iodine – a crucial step in thyroid hormone biosynthesis. More remarkably, when transplanted into athyreotic mice, these follicles fully functioned to restore normal thyroid hormone synthesis. These experiments proved that regenerative therapy for hypothyroidism was a possibility but, because of the transcription factor overexpression strategy employed, would probably not be clinically applicable.

To identify the actual differentiation pathway employed by ESCs or iPSCs to become follicular cells, our group has used a directed differentiation approach that uses growth factors thought to play a role in thyroid gland development *in vivo*. To enhance our ability to detect endodermal cells that are destined to become follicular cells, we labelled the Nkx2-1 locus with a fluorophore, such that cells appearing green or red could be identified as expressing Nkx2-1.[3] Using this technique we were able to identify that the growth factors bone morphogenic protein 4 (BMP4) and fibroblast growth factor 2 (FGF2) were absolutely required for endoderm derived from mouse ESCs to become thyroid follicular cells. Furthermore, both BMP4 and FGF2 appeared to play a similar role in *Xenopus*, suggesting that this pathway is conserved across species.

Once specified with BMP4 and FGF2, Nkx2-1 positive cells could then be further differentiated in a 3D culture system into follicular units that expressed all important thyroid markers, including thyroglobulin, and more importantly had the ability to synthesise small amounts of T4.

SEEKING SUCCESS *IN VIVO*

To prove these cells could function *in vivo*, we transplanted ESC-derived follicles after 30 days in culture into the kidney capsule of mice that had previously been given ^{131}I to render them hypothyroid. At 2 weeks after transplantation, T4 began to reappear in the transplanted mice, and by 8 weeks almost all transplanted mice had become euthyroid. Importantly, the TSH set point returned to its pre-hypothyroid setting, demonstrating that the transplanted cells were entirely TSH-responsive.

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

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

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

'Given the progress in the field, it is fully expected that a directed differentiation approach using human iPSCs should be possible and that transplantable follicles will be produced.'

ANTHONY N HOLLENBERG
Currently Sanford I Weill Chair of Medicine and Professor of Medicine at Weill Cornell Medical College, New York, NY, USA

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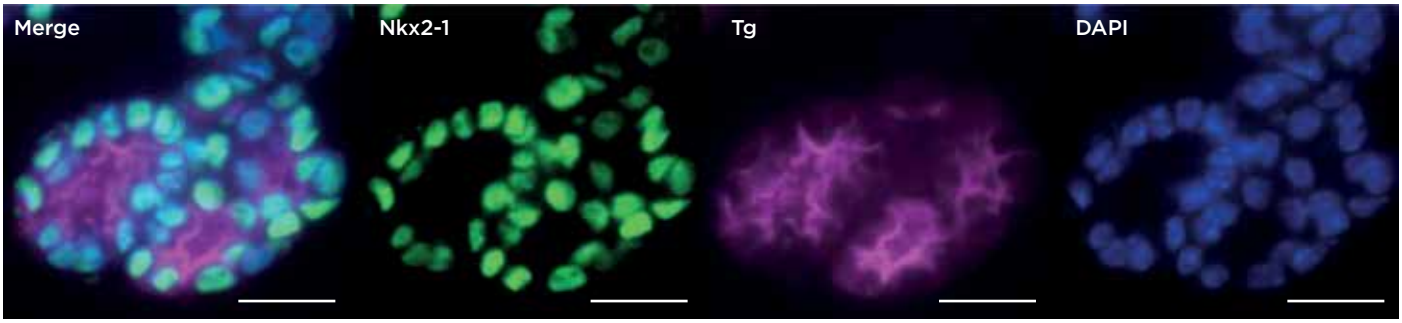

In vitro development of ESC-derived thyroid follicular cells by directed differentiation: immunofluorescence microscopy of day 30 follicular-like structures after immunostaining for Nkx2-1 and thyroglobulin (Tg). Nuclei are counterstained with DAPI; scale bars 10μm. Reproduced with permission from Figure 5F, Kurman *et al.* 2015 *Cell Stem Cell* **17** 527–542

Celebrating and rewarding EXCELLENCE IN ENDOCRINOLOGY

Join us in congratulating our 2020 Society medal recipients, world leaders in endocrinology, whose work continues to advance our knowledge and clinical practice in endocrinology. Our medallists will present plenary lectures at SfE BES 2020 on 16–18 November in Harrogate.

MEDAL LECTURERS

DALE MEDALLIST
Professor Dame Frances Ashcroft

SOCIETY MEDALLIST
Professor David Ray

STARLING MEDALLIST
Professor Davide Calebiro

TRANSATLANTIC MEDALLIST
Dr Daniel Drucker

EUROPEAN MEDALLIST
Dr Nelly Pitteloud

INTERNATIONAL MEDALLIST
Dr David Mangelsdorf

JUBILEE MEDALLIST
Professor Anne White

HELP CHOOSE OUR 2021 MEDALLISTS

Who do you think deserves to be recognised for their contributions to our field next year?

For more details and to nominate, visit **www.endocrinology.org/grants-and-awards/prizes-and-awards/medals**.

The deadline for nominations is **10 July 2020.**

INTRODUCING THE NIKKI KIEFFER MEDAL

In honour of Nurse Member Nikki Kieffer's huge contribution to our Society, the Endocrine Nurse Award will be renamed the Nikki Kieffer Medal from 2021.

Nikki was the inaugural winner of this Award and sadly passed away in 2019. She played an important role in the Society, serving as Chair of the Nurse Committee, leading the development and publication of the *Competency Framework for Adult Endocrine Nursing* and championing the creation of the Society for Endocrinology–Oxford Brookes Masters-level module in Endocrine Nursing.

SfE BES 2020
16-18 November
HARROGATE

SfE BES 2020 WHAT DOES IT HAVE FOR YOU?

It has never been more important for us to connect to our community. We hope to be able to see each other in person in Harrogate, but we are currently exploring virtual alternatives, to enable us to bring you the latest in endocrinology, in the safest possible way. We hope to come together, in some form, to share the latest developments in endocrinology and learn from our experiences over the last year.

We have created a programme which bridges the gap between research and clinical practice, whilst providing an update on current best practice and cutting-edge science.

FOR EVERYONE

'WHAT IS NEW?' SESSION

Start the Conference off with a review of the latest developments in clinical and basic endocrine research. This session will give you a valuable update on cutting-edge science, providing a useful context for the next three days.

PLENARIES AND MEDAL LECTURES

Hear from world-leading researchers as they discuss their work and how it has transformed our understanding of endocrinology.

SYMPOSIA

Our symposia cover the whole spectrum of endocrinology and this year include lifestyle and metabolic disease, nuclear and G-protein receptor physiology, NET immunotherapy, and cutting-edge single cell transcriptomics.

ENDOCRINE NETWORK SESSIONS

2020 will see the return of the Endocrine Network sessions. These interactive sessions will give you the chance to discuss the recent developments in your subspecialty.

Attend an Endocrine Network session to interact with your colleagues, build collaborations and start new projects.

There will be one session for each of the Society's Endocrine Networks:

- Adrenal and Cardiovascular
- Bone and Calcium
- Endocrine Consequences of Living with and Beyond Cancer
- Endocrine Neoplasia Syndromes
- Metabolic and Obesity
- Neuroendocrinology
- Reproductive Endocrinology and Biology
- Thyroid

FOR SCIENTISTS

BASIC PHYSIOLOGY WORKSHOP

Learn about the latest research techniques and model systems. Hear from pioneering scientists as they explain how to use these new tools to further your research.

BASIC SKILLS SESSION

Expand your skill set outside the laboratory with our Basic Skills session. This year's session focuses on writing successful funding applications and effectively managing teaching commitments.

FOR CLINICIANS

MEET THE EXPERT SESSIONS

Learn from experts working in endocrine clinics every day as they explain the solutions to both common and complex problems. These highly informative sessions also include a question and answer section, meaning you can get the specific advice you need. Meet the experts and return to your clinic with the knowledge to face new challenges.

'HOW DO I?' SESSIONS

These talks are on focused clinical problems. 'How Do I?' sessions help you to investigate and manage challenging endocrine cases, providing you with the information you need to better care for your patients.

CLINICAL MANAGEMENT WORKSHOPS

This year focusing specifically on pituitary disease and reproductive health, these workshops offer solutions to clinical challenges and help to widen your perspective on disease. Join these sessions to enhance your knowledge and further your understanding of our field.

FOR NURSES

NURSE SESSIONS

These sessions are chaired and led by nurses and focus on a specific theme or topic using case presentations. These sessions feature experts in the field and are designed to give you the knowledge you need to improve patient outcomes.

We have designed the programme to avoid clashes with other valuable clinical content such as How do I? sessions, Meet the Expert sessions and Clinical Workshops.

THE NURSES' LOUNGE

The Nurses' Lounge offers a nurse-only space where you can network with colleagues from across the UK. Members of the Society's Nurse Committee will be on hand during breaks on Tuesday to introduce you to our endocrine nursing community. Whether you are joining us for the first time or looking to reconnect with old friends, you are welcome to join us.

FOR EARLY CAREER ENDOCRINOLOGISTS

THE EARLY CAREER SESSION

Attend the Early Career session for guidance and advice on how to advance your career in endocrinology. Together we will explore the options available to you, whether you are interested in research, teaching, leadership roles or clinical practice.

THE EARLY CAREER LOUNGE

Located at the heart of the exhibition, the Lounge is a friendly and open space where you can meet with your peers. Members of the Early Career Steering Group will be available during breaks on Monday to help you connect with colleagues; this makes the Lounge especially useful if you are travelling on your own or are attending for the first time.

EARLY CAREER CURRY AND QUIZ

Don't forget to sign up for our famous Curry and Quiz. This event gives you a chance get to know your colleagues in a fun, informal setting. Each team is captained by a senior endocrinologist, giving you the chance to get acquainted with leading figures. The quiz is great for first-time attendees as there is always somebody to chat to.

This free event is very popular and places are limited, so don't forget to add the quiz to your booking whilst registering.

MAKE CONNECTIONS WHICH WILL FURTHER YOUR CAREER

No other UK meeting gives you as many opportunities to connect with endocrinologists who share your research interests. SfE BES brings together the endocrine community in an open and friendly forum where the latest developments in the field can inform and inspire your work.

"In the early years of my SfE BES attendances, I was privileged to be granted a wealth of opportunities to meet colleagues from across the country with similar research interests to me. The networking led to collaborations which would not have readily materialised without this forum. The fact that the meeting is relatively small compared to some other specialty meetings definitely creates a friendlier environment and facilitates collaboration and partnership.

Attending SfE BES for me is like coming home, it has given me such pleasure over the years and I leave each meeting with a wealth of new knowledge and experiences, and a warm glow!

DR ANNICE MUKHERJEE
Salford Royal NHS Foundation Trust & University of Manchester

"Being at the conference gave me the chance to meet and set up a partnership with Bijay Vaidya, which improved my data and led to a good paper. This paper improved by this collaboration was key to me getting an MRC Fellowship to study for an MSc in epidemiology at the London School of Hygiene and Tropical Medicine. This led to further papers and a Young Investigator Award at SfE BES 2 years later.

Looking forward to where SfE BES leads me next!

DR PETER TAYLOR
Cardiff University

REGISTRATION AND ABSTRACT SUBMISSION ARE NOW OPEN!

ABSTRACT SUBMISSION DEADLINE:
Monday 24 August 2020 (11:59pm BST)

TRAVEL GRANT APPLICATION DEADLINE:
Wednesday 16 September 2020 (11:59pm BST)

EARLY BIRD REGISTRATION DEADLINE:
Thursday 15 October 2020 (11:59pm BST)

Visit **www.endocrinology.org/sfebes2020** to learn more

managed by **bioscientifica**

iNternationality

WRITTEN BY TONY COLL

FIRST PUBLISHED IN ISSUE 106 (2012/13)

So I got myself an iPhone*. I have moved on. Tired of being mocked by children, colleagues and strangers on the train about the Old World device that had served me so well for so many years, I have entered the polyphonic world of global glee.

Things are different now. Never mind the neuroendocrinology behind the addiction to check persistently if I have another message of international, day-stopping importance (…what do you think?), my upgrade has imbued me with a range of superpowers.

I seem not only to be able to end a call with my chin, but also to be able to alert the emergency services at the same time as unlocking the screen. I can now chuckle ironically to myself as, head down, looking at a blue dot in a palm-sized glow world to find out where I am, I walk into a lamp post. Such fun.

In truth, my critics were right and there is no going back. It is a palpable joy to be able to find information so readily in whichever unlikely place you find yourself. The world has never seemed so small and with open access so correctly on the rise, data are but a finger flick away.

Yet there remains a need to interact and communicate in a way that cannot be done though a keypad. I discovered today on a news website that if my new technological world leaves me feeling cold I can get myself a 'wearable social media vest' (**www.bgr.com/2012/10/05/like-a-hug-jacket-facebook-likes**). A 'like' on a well known social networking site will, via wireless technology, inflate said jacket and you will be 'hugged'. Pretentious whimsy perhaps, but maybe the artist is hinting at something a little deeper, in that, however advanced the augmented reality of technology becomes, sentient humans require more than visual input to make sense of – and feel they belong in – the world.

People still need to meet in the flesh. Consider some of the projects you are working on. How much easier do things run if you have met your collaborators in person to discuss what is going on? Reflect a little upon the power of the corridor conversation to point you in a different direction. The same is true of conferences; watching the story 'played live', then discussing the finer points with your mates afterwards, can be far more rewarding than sitting in an office hunched over a 10-inch tablet. The rush of delivering a cracking talk to an appreciative audience should also be celebrated.

The Science Committee plays a major part in shaping the contents of meetings throughout the year. We come together and discuss how you as an endocrine community can do the same. We are not a closed shop of self-interested parties, but strive to put together quality programmes of decent science from wherever it originates. As you travel the world, be it real or virtual, and come across exciting and interesting endocrinology, let us know via whichever medium you have to hand and we'll see if we can help spread the news.

TONY COLL

**Other highly connected, electronic hand-held devices are available.*

KITE SURFING: 10,000 HOURS AND MASTERY

WRITTEN BY JOHN NEWELL-PRICE

FIRST PUBLISHED IN ISSUE 109 (2013)

Have you ever tried kite surfing? You have to marvel at this improbable activity and the extraordinary skill, style and panache displayed by the riders. Those attending ENDO 2013 in San Francisco will have been treated to the sight of swarms of the multicoloured kites highlighted by the late evening sun, set against the iconic Golden Gate Bridge silhouetted in the distance.

Every second, a series of extraordinary skills is coalesced in order to execute this mind-boggling pastime: skimming across the water whilst balancing on a plank that has no buoyancy; controlling a kite that generates sufficient force to be capable of catapulting the operator tens of metres into the air and dislocating all manner of joints; being hyperaware of all opportunities to refine speed and poise; responding to shifting wind directions; and avoiding obstacles, including other water traffic … and the occasional shark!

How would you go about acquiring this alien skill? You might gain some insight by watching some YouTube videos and spending evenings researching kit and technique. However, ultimately, you'd have to take the plunge: sign up for some lessons, and, importantly, get wet. Initial attempts would be challenging, scary and frustrating, but with perseverance, correct guidance and, most importantly, dedicated practice and application, you would eventually be an expert.

In the face of limited availability of time, if you really concentrated on technique on every occasion that you went out on the board, the level of your mastery would increase greatly, and more quickly. Back this up with theory of the technique, and the results would be even quicker. With the right exposure and luck you might even get a sponsorship deal, join the world competition circuit and be chosen to grace a Red Bull advert – whilst for most people simply participating in the sport would be an excellent and rewarding end in itself.

You will have recognised this thinly veiled analogy to medical specialist training. Expert clinical endocrinologists are the kite surfers of the medical world, integrating reams of data in a careful and timely manner with the necessary great attention to detail, and using knowledge and skilful clinical acumen that other specialties frequently wonder at.

Reaching such status is, however, under threat. Currently, a major source of frustration is the detrimental effect on endocrine training caused by the demands of the acute medical take and continuing care. The solution to this very important problem lies outside the control of endocrinology, as it can only be solved by multi-specialty re-engagement with general internal medicine, so sharing the burden that all too often falls disproportionately on our trainees. This issue is high on the agendas of the committees of the Society for Endocrinology and Royal Colleges, but will take time to resolve.

The oft-quoted 10,000 hours needed to master any discipline is relevant, with the distinction between competence and mastery being key. Early on there is a steep learning curve, whilst the latter part is finessing. It's a long time: one that for many will extend beyond clinical specialist training. Of course, not all experience is equal, and some areas are easier to master than others.

How then, today, does one maximise the opportunities to learn and gain experience in the current time-limited training environment? One answer is the postgraduate course. For example, the Society for Endocrinology runs the excellent and highly rated Clinical Update, an annual 3-day residential course that covers the training curriculum over 3 years, and where participants have the opportunity to closely interact with, learn from, and challenge experts in their field: experts who are so motivated to teach and impart knowledge and transfer skills that they give their time freely and generously in what are always hectic schedules.

Courses are important, but are not the complete solution. There is one very simple, free, and time-efficient strategy that can be used to maximise the experience of clinical training, but one that has, perhaps, become less commonly practised – learning from each and every patient. By this I do not mean to invoke some trite soundbite that might appear in some educational rubric, nor a series of acronyms beloved of the Annual Review of Competence Progression (ARCP) process, such as Case-Based Discussions (CBD), mini-Clinical Evaluation Exercises (miniCEX) and Direct Observation of Procedural Skills (DOPS).

No, I am simply stating that, for every single patient that one has not seen personally before, the set of notes (especially if thick) should be opened at page one, and read … to completion. This takes some time but always yields results, and with practice the skill becomes quicker. Unanswered issues (e.g. imaging, biochemistry and pathology) are then chased up and a complete picture generated. It is surprising how often this is not done, and then how rapidly answers to a clinical problem appear when it is. Add in background reading for a given condition, and, like the emerging kite surfer dedicated to practice, mastery grows organically.

JOHN NEWELL-PRICE
Professor of Endocrinology and Honorary Consultant Physician, University of Sheffield

FLUCTUATING BODY COUNT IN THE DIAGNOSIS AND MANAGEMENT OF AN ENDOCRINE DISORDER

Keen readers of *The Endocrinologist* may remember our occasional contributor, Hotspur. He has recently seen his last ever endocrine patient and sent us the story. We thank him for all his contributions and wish him well for the future…

Throughout medical history, numerous men and women are remembered for their great scientific and clinical contributions. Diseases were named after the early, if not earliest, observers, e.g. Cushing, Addison, Graves, etc., who reported specific conditions. Alas, this no longer occurs.

Personal success stories are still evident and in every Society for Endocrinology BES conference there are award lectures, in which individuals are honoured for their scientific/clinical contributions. It is clear from the content of these lectures, however, that a team effort is involved, when a lecturer finishes his/her talk with a slide listing the 10 or 15 individuals who contributed to the success of the work.

Professional fame within medicine is no longer feasible for a solitary individual. I mulled over this sad realisation, whilst in quiet retirement in an old mill in middle England. Curiously, it was here that I sensed a last chance might have come my way for a Hotspur symptom/sign to enter the medical literature. Medical is stretching it a bit, as my subject was a cat called Bruce, who belonged to one of the families that lived in the seven residences at the mill.

Bruce was an assassin who killed squirrels, voles, rats and young rabbits on a daily basis. Those executed were easy to count, as the bodies were deposited on the doorsteps of many of us who lived at the mill. The killing and showing off over the bodies were consistent and relentless. Even bank holidays were not recognised as days of rest. Therefore, when the killings ceased completely for several months, it was clear to me that something was up. It was then that I suddenly appreciated that my career would not be ending with a whimper, more like a meow. Here are my observations. Bruce had either lost the desire to kill, or ability to execute a kill, or both. Furthermore, Bruce was an old cat and looked a bit ragged. Epidemiologically, I knew that around 10% of elderly cats acquire some form of thyroid dysfunction. No-one else, to my knowledge, had put forward the suggestion that the desire and capacity to kill might be lost through the development of thyrotoxicosis. So Hotspur had made an original 'clinical' observation. Setting up human studies to challenge this hypothesis would take too long. Anyway, which known assassins would be likely to participate in a study in which the active arm might threaten their employment prospects?

My suggestion that Bruce have his thyroid function tests checked was quickly taken up by his owners and, to my delight, Bruce was thyrotoxic. Subsequently, he received anti-thyroid drug medication and, within months, put on weight and looked more energetic. His owners had his thyroid function tests checked regularly to determine if he was now euthyroid. I, of course, did not need to see the test results, as, reassuringly, the bodies were once again piling up on my doorstep. In truth I felt happy, not especially because of Bruce's recovery, but because the newly described Hotspur's symptom/sign had become an established fact, at least in this part of the world. Hotspur had achieved his personal fame, albeit by a whisker!

HOTSPUR

Supporting each other IN UNPRECEDENTED TIMES

COVID-19 marks a watershed moment in history. Many of us have had to change our way of working, beyond going digital, and we have done so with great enthusiasm and spirit. If we have learnt anything in the past few weeks, it is the power of collaboration and creativity. We want to support our members and colleagues in the endocrine community as best we can through the current crisis and beyond.

A MESSAGE FROM SOCIETY PRESIDENT RAJ THAKKER

I very much hope that you and your families are safe and well in these troubled and difficult times due to the COVID-19 pandemic.

During these challenging times, the Society for Endocrinology and its members have been engaged in many personal, professional, and learned society activities for the immediate and future benefit of our patients and nation. What is also clear is that the endocrine community is coming together like never before, to quickly meet these challenges in response to the COVID-19 crisis. We should all take pride in these immensely generous contributions, and I would like to thank all of you and to highlight some of these achievements.

On a personal level, many of our clinician and nurse colleagues have been redeployed to work on the COVID-19 crisis front line and provide care, under unimaginably difficult and stressful circumstances, whilst ensuring their endocrine patients are not forgotten. Our scientist colleagues have volunteered to provide testing for COVID-19 whilst shutting down their own research programmes, and many are also working as volunteers in local communities. A special thank you to all of you for all your hard work.

We also updated our adrenal crisis page with COVID-19 advice, sick day rules and a downloadable copy of the new steroid card, now including advice for children.

At the national and international levels, many colleagues have been providing leadership and expertise in preparing strategies, reports and guidelines for UK Royal Colleges and Government (e.g. the Royal College of Physicians (RCP), the Academy of Royal Colleges, NHS England (NHSE) and Public Health England), international journals (e.g. the *European Journal of Endocrinology* and *Journal of Clinical Endocrinology & Metabolism*): and patient groups. At the same time, we are finding solutions for sharing best practice, and providing virtual training for our early career colleagues.

The Society is more important than ever at this time, in providing a platform not only to join up and support this work, but also to make it stronger by feeding in views from the membership. Working together has allowed us not only to respond very quickly and effectively to immediate challenges but also to seize important opportunities that will impact our specialty for decades to come. I was involved in the Society's response to the RCP on plans for maintaining vital elective care during the COVID-19 crisis and planning for a relaunch of services. I feel very privileged to work with such splendid and marvellous colleagues, whose response to the appeal was unique, with well thought out and constructive comments. This work enabled us to plan our own proposal on 'The future of endocrinology: Restoring current services and rethinking the future provision of endocrine care across the UK'. The successful implementation of this proposal will require establishment of a working group and input from all Society members. Similar plans for provision and development of research and training in science will follow later.

During the past weeks of 'lockdown' I have reflected on the turn of events for our Society. The original ambitious plans I might have had for my presidency may not happen as I envisaged. However, I am confident that the Society will not only survive COVID-19 but will come out of it stronger than ever before because of you, its members, who are erudite, energetic, collaborative and highly proficient professionals. As we seize and drive forward the agenda for change, we are fulfilling like never before our Society's mission to advance scientific and clinical education and research in endocrinology for the public benefit. Let us all work together to deliver this bold vision and provide a better and brighter future for the next generations.

A MESSAGE FROM IAN RUSSELL, CHIEF EXECUTIVE

The COVID-19 pandemic is having a huge impact on everyone and, of course, the Society is no different. We have had to rapidly adapt our own operations to be able to continue our work from home, to reprioritise and, where necessary, change the way we deliver our services, as we attempt to ensure that we can continue to provide the most effective support for our members. We are fortunate to have been able to do all these things relatively quickly and efficiently, thanks to our organisation's resilience and our responsive Committees and Council.

The Society's most important job – at all times, but particularly in times of crisis – is to be responsive to the needs of our members and to keep pace with how these change over time. I am immensely proud of, and grateful to, the individuals within our Committees, Council and Officer teams who have worked tirelessly over the last few weeks, showing commitment beyond expectation, to listen to our members and address these challenges.

A number of new and important initiatives are being taken forward (as detailed on the following pages) to address training, service relaunch and sharing best practice. We are learning very quickly as we move more activities onto virtual platforms and put in place solutions for immediate needs. While this is a difficult time for all of us, the determination and collaboration being shown presently will no doubt make the Society fit for purpose not just now but well into the future.

UPDATE FROM STEPHANIE BALDEWEG, CHAIR OF THE CLINICAL COMMITTEE

I want to thank you all for your response to the coronavirus (COVID-19) pandemic. I wish to thank you for your dedication, passion and tenacity in keeping our endocrine patients safe and our endocrine community collaborative and supportive.

Here was the challenge: to share information and provide guidance across primary and secondary care for treatment of endocrine conditions during this fast moving pandemic of a fairly unknown virus. It has even been called 'invisible'. We aimed to share information to help manage our patients as well as to offer support to colleagues and patient groups. In response to the COVID-19 crisis, your Society's Clinical Committee is working very hard to support the endocrine community, doctors, nurses, scientists, GPs, patient support groups and our patients during this challenging time.

'Our resource page has received some great feedback, both nationally and internationally, and feedback on individual documents has shown us how much these are valued by both the professional and patient communities.'

We had two main initiatives:

- Firstly, we needed resources on how to manage chronic/elective care with reduced access to staff, rooms, phlebotomy and imaging. This included prioritisation of conditions and deciding what was time-dependent and what could safely be postponed.
- Secondly, we needed resources on how to manage patients with endocrine conditions who are acutely unwell with the COVID-19 virus.

We wrote to all our members, inviting them to send their resources to us and, as each came in, we reviewed them quickly. This ensured the advice made available on our website was appropriate and as current as possible. Although the resources are not Society-endorsed, they have been approved by the Clinical Committee, for sharing, as part of our rapid response to clinical practice management during the COVID-19 crisis. To have this information easily accessible, we created a COVID-19 resource page, updating it as each new resource or recommendation became available.

We are also liaising with the RCP, NHSE, RCGP, ABCD, ADSHG, The Pituitary Foundation and other Society-approved Patient Support Groups to ensure rapid exchange and dissemination of important advice and information.

Our resource page has received some great feedback, both nationally and internationally, and feedback on individual documents has shown us how much these are valued by both the professional and patient communities. Our early advice inspired the commissioning of a great series of articles in *European Journal of Endocrinology* on managing endocrine conditions during COVID-19. Access them at **www.bioscientifica.com/publishing/covid-19-collection**.

View adrenal crisis advice at **www.endocrinology.org/adrenal-crisis**

Looking ahead, we are also starting careful planning for reintroduction of our delayed elective work, and we are working on a proposal on how our change in practice can influence the future of endocrinology.

As a Society, we are committed to supporting our members and their patients and, as always, are very grateful for your input and support. I am especially appreciative of the members of the Clinical Committee and the Society Officers, who have made this ongoing project such a success and something we can all be proud of. I wish to thank you, the endocrine community, again for all the support, creativity and enthusiasm you have offered during the time of COVID-19. I am looking forward to a time when we can all meet again. Until then, stay safe!

DEFINING THE FUTURE OF ENDOCRINOLOGY WORKING GROUP

As resources start to free up, clinical services need to be relaunched at pace. Our current service models need radical change, with better use of digital services, new service models, streamlined referral and better integration with primary care.

We now have a once in a lifetime opportunity to innovate and to create endocrinology services fit for the 21st century and beyond. The Society for Endocrinology is going to be at the front of this transformation, and has set up a working group to define how endocrinology services should be delivered in the UK. The group will report to Society's Clinical Committee and will consult externally as required. All members will have the opportunity to contribute and final recommendations will be put forward to all relevant organisations in the coming months.

View the latest COVID-19 resources at
www.endocrinology.org/covid19

and submit yours to
clinical@endocrinology.org for review

UPDATE FROM KEVIN MURPHY, CHAIR OF THE SCIENCE COMMITTEE

COVID-19 has proven a major challenge for science and scientists. Labs are shut, students locked down; microscopes, mass spectrometers and mice stand idle. Training opportunities and conferences have been cancelled. But work for many of us has increased: there are home schooling to deliver, caring responsibilities, teaching to convert for remote learning, contingency plans to put in place for the next academic year. Many of us are anxious about our health and the health of our loved ones, but also about our jobs and the shape of UK science in the future. There is more work to do, fewer hours in the day, and, given the recruitment freezes at many institutions, fewer of us to do it.

Even should universities reopen soon, some abandoned experiments may not be able to be restarted. Funding will not automatically be extended for all grants and studentships. Even large charities are having a difficult time. Limited funds may mean that rebooting a mouse colony or repeating a long term study that was terminated early is simply not possible. Human studies that have stalled may prove difficult to restart, as facilities focus on infectious disease and potential volunteers remain cautious. Staff on fixed-term contracts may not have the option of extending their project; they and students close to finishing are nervous about finding jobs when no one is hiring and networking is impossible by conventional means. Universities are predicted to lose a large chunk of their funding as overseas students stick closer to home, and the Government has made it clear that they do not see it as their responsibility to bail out the higher education sector. Science's cachet in such times may enable it to guide or act as a scapegoat for government policy, but the state of the post-COVID economy is unlikely to encourage profligate spending, and there are worries regarding whether COVID-focused funding may crowd out other concerns.

It is difficult to predict how the sector will be reshaped in our absence from our laboratories. There are likely to be some silver linings. The take up and acceptance of home working and flexible working hours are likely to increase, giving scientists greater control of how, when and where they work. Many of us might conclude that our work has not suffered from the cancellation of certain events and meetings, and happily carry on without them with nary a backward glance. While no one is yet banging pans for the scientists of a Thursday evening, the strong emphasis in the media on scientific evidence, and the huge interest of the general public in what previously might have been considered esoteric areas of research, can only be a positive development for science.

> ***'The Society is not immune to the economic downturn, but also recognises the importance of supporting its members. Early career scientists in particular are vulnerable, and we have made the decision to carry on funding our Early Career Grants at the same rate as in previous years.'***

So what can the Society and the Science Committee do to help? The Society is not immune to the economic downturn, but also recognises the importance of supporting its members. Early career scientists in particular are vulnerable, and we have made the decision to carry on funding our Early Career Grants at the same rate as in previous years. Where some of our awards which fund research visits and summer studentships become difficult to support, we will look to repurposing these grants to help our members. Wet-lab training is obviously difficult remotely, but we are piloting our new 'Research Skills Webinars: *Lab in your living room* series' that will allow scientists to learn new skills even while stuck at home. Where we can, we will circulate up-to-date information on funding and job opportunities. We know how difficult it is to conduct additional experiments in response to referees' comments, and will aim to limit the requirement for such studies during the review process at the Society's journals. It is too big a job to expect a single society to be able to ameliorate all of the disadvantages our members are facing, but, while pipettes sleep silently in their stands and, on abandoned desks, mould grows slowly in lonely 'You and Your Hormones' mugs, we hope to continue to act as advocates and champions for both established endocrinologists and the next generation of scientists.

RESEARCH SKILLS WEBINARS: *LAB IN YOUR LIVING ROOM SERIES*

For PhD, post-doctoral and early career researchers to learn and develop new or existing skill sets which will benefit their current and future research. These webinars with live Q&A encompass techniques and analyses ranging from whole-genome CRISPR-Cas9 screens to analysing data using 'R'. They will outline the methodology needed to design, run and analyse data. Including:

Differential gene expression analysis from RNA-sequencing data
Dr Ildem Akerman
University of Birmingham

Publicly available data sources, a practical example
Dr Fabio Sanna
University of Oxford

Genetic screens and functional genomics using CRISPR-Cas9 technology
Dr Stuart Morgan
University of Birmingham

Visit www.endocrinology.org/webinars for full details and timings.

UPDATE FROM ANNE MARLAND, CHAIR OF THE NURSE COMMITTEE

During this challenging period, the Society and Nurse Committee recognise the amazing work and dedication of all our endocrine nurses in the UK. We value your remarkable approach to a dynamically changing situation and we know so many of you have changed the way in which you practise, in order to protect and care for your patients. Nurses' support to patients has been incredible and fully appreciated by all our patient support groups. We know that, within your teams. nurses are developing and providing different patient pathways/resources to enable delivery of high quality care. This has included online/email/phone consultation services and, crucially, education for those patients with adrenal insufficiency who require increased replacement of medication if clinically indicated.

This has, without a doubt, been the most challenging situation we have ever experienced professionally, and some of you will have been redeployed to the front line. You will have seen colleagues in difficult situations and this challenge has been difficult and stressful. However, the essence of being a nurse will have shone through and provided comfort. PPE is now adequate; however it has proven to be a challenge. We urge all health authorities to always provide adequate protection to the whole workforce of health professionals and to provide adequate testing for COVID-19.

Amid the upheaval of the pandemic, nurses can use reflection to process their experiences and, as we enter the recovery stage, apply this knowledge to facilitate changes within clinical care pathways of endocrine patients. Also, research in regard to professional resilience is usually based on organisational crises, such as nursing shortages. Possibly this crisis may lead to nursing research into organisational resilience during emergencies?

'Amid the upheaval of the pandemic, nurses can use reflection to process their experiences and, as we enter the recovery stage, apply this knowledge to facilitate changes within clinical care pathways of endocrine patients.'

These and other ideas for change are things to ponder for the future. As a Society, the support for nurse education and research is unwavering, through grants for practical skills, research, event attendance and training opportunities. Our Endocrine Nurse Update training is rescheduled for December 2020 but, in the meantime, we will also be looking for new, virtual ways to deliver training and networking to support our nursing community, who must pull together like never before.

NEVER SAY NO: MAKING THE MOST OF OPPORTUNITIES TO LEARN

WRITTEN BY MARIA RAVELO

FIRST PUBLISHED IN ISSUE 125 (2017)

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

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

THE POWER OF NETWORKING

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

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

GAINING EXPERIENCE

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

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

'From that moment, the networking doors opened for me! I was able to attend my first conference, learned more about the Society for Endocrinology and created important links at the same time.'

TAKE EVERY OPPORTUNITY

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

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

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

I couldn't contain my excitement and, indeed, I was not disappointed. On the first day, I was immediately introduced to the team and had a tour of the department. My timetable for the 3 days of work experience was followed through, with plenty of room to adjust it as necessary. I could switch to different clinics of interest, and every person on the team made me feel welcome. We went through different pathways, protocols and procedures, which I found very useful. Although there were some differences in terms of practice (e.g. growth hormone pathways and funding), it was helpful to witness how another centre operated and how they provided safe and efficient delivery of care to their service users.

LEARN ON YOUR FEET

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

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

MARIA RAVELO
Endocrine Specialist Nurse, East Sussex Healthcare NHS Trust

Images by ENDOCRINOLOGISTS

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

If so, our 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*.

This issue's photo was taken by taken by the Expedition Ice Maiden team, whom endocrinologist Rob Gifford studied during the first all-female unassisted Antarctic crossing. Rob said 'Despite austere conditions and mean weight loss of 10kg over the 1,000km ski traverse, the team demonstrated preserved pituitary, adrenal and ovarian function.'

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

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

Deadline for news items for the Autumn 2020 issue: **17 July 2020**.

Improving Patient Care

In Uncontrolled Acromegaly (IPCUA)

A Pfizer grant programme to support improved management of patients with uncontrolled acromegaly across the UK

- Apply between 23rd April and 28th September 2019
- Run by Pfizer Ltd, the grant programme is committed to excellence in improving the management of patients with uncontrolled acromegaly
- We are inviting applications for Medical and Educational Goods and Services (MEGS) grants from healthcare organisations in the UK.

To learn more and submit an application, visit:
https://www.pfizer.co.uk/medical-and-educational-goods-and-services-megs

To contact Pfizer for any other purpose, including adverse event reports or medical information requests, please call: 01304 616161.

PP-RDP-GBR-0127
Date of preparation - April 2019