ALL CHANGE FOR 2015!
Your Society calendar transformed  
P22

GOOD NURSING PRACTICE
A curriculum for group education  
P26

NEW! FREE E-LEARNING
Society journal leads the way in CME  
P28
As another year in this great endocrine world draws to a close, we can start to reflect on our own year’s scientific successes and failures. I don’t know about yours, but my 2014 seems to have flown past! As the nights draw in, I find myself contemplating the important questions in life – such as who will win Sports Personality of the Year (Lewis Hamilton or Rory McIlroy?). In truth, I think we are lucky to be part of such a rewarding specialty – the fact that we slip through the calendar so quickly must mean we are having fun.

As we gather round the hearth with our copies of The Endocrinologist, eat too many chocolates, watch rubbish TV (apart, of course, from the Doctor Who Xmas Special) and argue with our families, we are safe in the knowledge that another exciting endocrine year awaits us in 2015. With a general election campaign brewing, Ed and Dave will each promise us that their party is definitely the best. We all know that, whoever gets in, we will carry on breaking the boundaries of clinical and academic endocrine science regardless.

I think this exciting issue of your magazine, which looks at the impact of genetics in our discipline, has come together really well, and has a great balance of basic science and clinical endocrinology. Since Watson and Crick discovered the structure of DNA, the parallel technological revolution has allowed us to determine the entire human genome and develop beautifully sophisticated molecular research techniques. But what has it ever done for us as endocrinologists? Within these pages, we try to answer that awkward question.

So dear readers, let us charge our glasses, be upstanding, and drink a toast to another brilliant year of endocrinology. Here’s to the next one!
Applications are now invited for Editor-in-Chief for Journal of Endocrinology and Journal of Molecular Endocrinology for a 5-year term of office, commencing in August 2015. Applications are due by 1 February 2015 and more information is available via http://bit.ly/1ueqMom.

Society President Stephen O’Rahilly (Cambridge) will be awarded the 2015 European Hormone Medal by the European Society of Endocrinology and Society member Robert Semple (Cambridge) will be awarded the 2015 European Journal of Endocrinology Prize. Both will give invited lectures at the 2015 European Congress of Endocrinology in Dublin in May 2015.

Society member Rachel Batterham (London) has been awarded the Lilly Scientific Achievement Award by The Obesity Society.

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

SOCIAL FOR ENDOCRINOLOGY OFFICIAL JOURNALS

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

JOURNAL OF ENDOCRINOLOGY

Murine model of relative adrenal insufficiency
The hypothalamic-pituitary-adrenal (HPA) axis is essential for responding to stress through production of glucocorticoid hormones. Critically ill patients can display reduced cortisol concentrations and impaired responses to cortisol for the severity of their symptoms. 'Relative adrenal insufficiency' (RAI), this condition is hard to define and its reported incidence varies greatly depending on the patient population studied and the diagnostic criteria used. Several factors have been implicated in RAI, including altered HPA axis activity, adrenal steroidogenesis and plasma protein binding.

Livingstone and colleagues investigated involvement of altered glucocorticoid clearance and subsequent disruption of the HPA axis as a mechanism that facilitates RAI. Mice deficient in 5'-reductase type 1, a liver enzyme responsible for inactivation and clearance of a substantial amount of circulating corticosterone, were found to have impaired corticosterone responses following stress or adrenocorticotropic hormone administration.

This indicates that impaired glucocorticoid clearance can alter the HPA axis through feedback mechanisms and has important implications for management of patients with RAI and those receiving 5'-reductase inhibitors for prostatic disease.

Read the full article in Journal of Endocrinology 222 257–266 (OA)

JOURNAL OF MOLECULAR ENDOCRINOLOGY

p38 MAPK in age-related alterations in steroidogenesis
Ageing in humans and animals has been associated with a general decline in steroid hormone production. This is apparently not caused by a reduction in hormone signalling or defective steroid hormone-synthesising enzymes. There is evidence that cholesterol availability reduces with age due to deficiencies in the ability to translocate cholesterol to the inner mitochondrial membrane where it is initially converted into steroid hormones. Reactive oxygen species and associated damage to STAR, a protein complex that mediates cholesterol transport to the inner mitochondrial membrane, may account for age-related changes in steroidogenesis.

Zaidi and colleagues have defined a pathway involving p38 mitogen-activated protein kinases (MAPKs) that leads to the inhibition of STAR gene expression. This pathway was induced by oxidants in cell lines. The authors have therefore defined a pathway that may account for the reduced biosynthesis of steroid hormones during ageing, although further studies are required to test its significance in animal models and humans.

Read the full article in Journal of Molecular Endocrinology 53 1–16

ENDOCRINE-RELATED CANCER

Breast cancer risk, night work and circadian clock SNPs
Circadian rhythm, the ~24-h biological clock, is important in the adaptation of physiological processes to the day/night cycle. Disruption of the circadian rhythm through shift work has been associated with many adverse biological effects.

Truong and colleagues investigated the association of disrupted circadian rhythm with breast cancer. In a population-based case-control study, they assessed the presence of single nucleotide polymorphisms (SNPs) in 23 circadian clock genes in night shift workers. The authors identified two SNPs in a potential tumour suppressor gene, RORA, associated with breast cancer in the whole population and in postmenopausal women. However, a clear interaction between breast cancer risk and circadian genes in night shift workers was not identified.

The association of SNPs in circadian pathway genes with the occurrence of breast cancer does however indicate that further investigation of the role of the circadian rhythm in breast cancer is warranted.

Read the full article in Endocrine-Related Cancer 21 629–638

ENDOCRINE HIGHLIGHTS

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

Birth month and autoimmune thyroid disease
One of the great unanswered questions of general medicine is ‘What are the triggers for autoimmune disease?’ Viral or bacterial infection has often been postulated as a precipitant for thyroid disease, so is there a relationship between the time of year or season of onset, fluctuations in potential precipitants, and timing of birth, which may have an effect on subsequent immune system development?

Hamilton and colleagues analysed three large European datasets of Caucasian patients to determine a relationship between birth month and onset of Graves’ disease and Hashimoto’s thyroiditis. Whilst no clear relationship for Graves’ was uncovered, there was the suggestion that for some birth months (in the autumn) there is a slightly higher rate of Hashimoto’s for females patients in the OXAGEN AITD Caucasian Family Collection.

Read the full article in Journal of Clinical Endocrinology & Metabolism 99 E1459–E1465 (OA)
Parental origin of X chromosome and aortic stiffness in Turner syndrome

Women with Turner syndrome can suffer from increased aortic abnormalities, meaning they are at higher risk of cardiovascular complications that can contribute to higher morbidity and mortality rates.

Abd-Elmoniem et al. set out to examine whether there was a relationship between the parental origin of the X chromosome and the aortic stiffness in these patients. The group conducted a cross-sectional study on 24 patients with Turner syndrome. Patients whose X chromosome was inherited from their mother had significantly stiffer aortas compared with those whose X chromosome had a paternal origin.

This is the first study to suggest that aortic stiffness in women with Turner syndrome may be due to the origin of their X chromosome. The findings indicate that parental chromosomal analysis and aortic stiffness measurements may be useful in the risk assessment and clinical management of Turner syndrome patients.

Read the full article in Clinical Endocrinology 80 467–470

An unusual cause of bilateral adrenal gland haemorrhage

Gowda et al. report the case of a 40-year-old man who was referred to a surgical unit for management of a large liver abscess. Three days after percutaneous drainage of 250ml of pus from the abscess, the patient presented with severe hypotension, requiring aggressive fluid resuscitation and hydrocortisone support.

A CT scan of his abdomen revealed a significant decrease in the size of the abscess, along with a bilateral adrenal gland haemorrhage (BAH). Assays confirmed the patient had extremely low cortisol (15nmol/l) and undetectable aldosterone (<70pmol/l), indicative of primary adrenal gland failure. Further investigation suggested he was also suffering from anti-phospholipid antibody syndrome (APLS), which can be a rare cause of BAH.

This case emphasises the need for strong clinical suspicion for diagnosing BAH, a rare but life-threatening condition, and its association with amoebic liver abscess and APLS.

Read the full article in Endocrinology, Diabetes & Metabolism Case Reports 2014 EDM140058 (OA)

Afamin, oxidative stress and PCOS

Polycystic ovary syndrome (PCOS) is a frequent cause of female infertility. Three main features are polycystic ovaries, hyperandrogenism and oligo- or anovulation. Familial inheritance has been linked to the aetiology of PCOS, as well as high levels of insulin. Recently, oxidative stress has also been suggested as a cause.

To investigate the diagnostic and prognostic effects of oxidative stress on PCOS, K"ONIGER and colleagues measured serum concentrations of afamin, a binding protein for the antioxidant vitamin E, in a cross-sectional study of 85 patients. Elevated afamin concentrations, found in PCOS, were correlated with body mass index, free testosterone index, homeostatic model assessment-insulin resistance, fasting glucose, and sex hormone-binding globulin. Overall, afamin indicated the presence of insulin resistance in patients irrespective of obesity.

This indicates that afamin concentrations could be used as an indicator of disorders of oxidative stress and inflammation associated with insulin resistance rather than a specific diagnostic marker of PCOS. Whether afamin is elevated in other disorders associated with insulin resistance remains to be determined.

Read the full article in Endocrine Connections 3 120–126 (OA)

‘Endocrinised’ FGF1 as a potent insulin sensitiser

Thiazolinediones are highly effective in treatment of type 2 diabetes, acting via peroxisome proliferator-activated receptor-γ to control adipogenesis, lipid metabolism and insulin sensitisation. The side effects associated with these compounds mean that alternatives are required.

Suh and colleagues investigated the use of ‘endocrinised’ fibroblast growth factor 1 (FGF1) as an insulin sensitiser. Using mouse models of obesity they found that single doses of FGF1 facilitated insulin-dependent lowering of glucose levels, which was independent of the effects of FGF1 on food intake. FGF1’s insulin-sensitising activity was shown to be mediated by FGF receptor 1 signalling and could be dissociated from the mitogenic activity of FGF1. There was no evidence of weight gain, liver steatosis or bone loss following FGF1 administration, which are established side effects of current therapies.

This provides promising evidence for FGF1 use in type 2 diabetes. Clinical trials in humans are required to fully assess the efficacy of FGF1 and to establish whether the promise of reduced side effects compared with current therapies is substantiated.

Read the full article in Nature 513 436–439

Ancestral endocrine disruptors alter rat stress reactivity

Endocrine disrupting chemicals (EDCs) are known to pass their toxic effects from one generation to the next. New research suggests that females with ancestral exposure to EDCs may be more prone to adverse stress responses than their male equivalents.

Gillette et al. have demonstrated that ancestral exposure to a fungicide, vinclozolin, which is commonly used in agriculture, may have long-lasting generational effects. Female rats whose great-grandparents were given vinclozolin became significantly more vulnerable to stress. This effect was not evident in males.

These female rats had dramatically higher corticosterone levels, and higher expression of genes associated with anxiety responses. It seems that as high corticosterone levels can affect memory and learning, this may be responsible for the altered stress behaviours observed in these animals. Furthermore, exposure to EDCs does not alter the animals’ genetic code, but changes the way specific genes are expressed. Consequently, these results suggest that further research is warranted on the effect of environmental contamination by EDCs on future human stress responses and behaviour.

Read the full article in Endocrinology 155 3853–3866

Risks and benefits of bariatric surgery

This review by Arterburn and Courcoulas summarises all the recent evidence relating to the safety, effectiveness and metabolic outcomes of bariatric surgery. Its aim is to guide clinical decision making. It seeks to assess which patient groups may benefit most from the different types of surgical intervention and, indeed, which individuals may be ‘cured’ of such conditions as type 2 diabetes, balanced against the potential harmful risks of undertaking major surgery in a sub-optimally fit population group. Added to this is the emerging evidence that some procedures are adversely associated with a higher risk of substance misuse disorders (perhaps replacing one addiction for another), suicide and nutritional deficiencies.

The authors conclude that, given the wide variation in outcomes, any decision to undergo surgery should be based on a high quality shared decision-making process.

Read the full article in British Medical Journal 2014 349 g3961

Endocrine connections

© Understanding Animal Research
Clinical genetics has become one of the fastest growing specialities. The fundamentals of medical research and clinical practice are increasingly based on the role that genes play from preconception to death – ‘womb to tomb’ – and perhaps even afterwards, thanks to forensic genetics and genealogy.

Before the use of modern laboratory techniques, many physicians documented clinical descriptions of genetic conditions, syndromes, and multiple congenital anomalies. Now with the molecular revolution, we can identify an accurate scientific basis behind these classical clinical descriptions.

In the UK there are currently 23 regional genetic centres. As a specialty, we provide diagnostic services and genetic counselling for individuals and families at risk of birth defects with an inherited basis, chromosomal abnormalities, single gene disorders and familial cancer susceptibility. The roles of the clinical geneticist are broadly: to diagnose affected individuals with Mendelian (single gene) conditions; to provide reproductive risk assessment with prenatal and pre-implantation diagnostic services; to reduce the burden of inherited diseases through screening and preventative strategies.

A BRIEF MODERN HISTORY OF GENETICS
Hippocrates speculated that ‘seeds’ were produced by various body parts and transmitted to offspring at the time of conception. Aristotle believed that male and female semen mixed at conception to create a new offspring derived from both parental factors. The modern idea of inheritance of genes can be attributed to the monk Gregor Mendel who published his work on pea plants in 1865. His work was largely ignored at the time, and it was only when it was rediscovered in 1901 that clinical genetics started to be thought of in its modern context.

In 1953, when Watson and Crick published the structure of the DNA molecule, linking the rules of inheritance to a double-stranded polymer capable of encoding information with alphabets of four chemical residues, the genetic revolution had truly begun. 1959 is termed ‘the wonderful year of human cytogenetics’ as it was in this year that residues, the genetic revolution had truly begun. 1959 is termed capable of encoding information with alphabets of four chemical residues, the genetic revolution had truly begun. 1959 is termed and 1966, Victor A McKusick first published ‘Mendelian inheritance in man’ (MIM), a comprehensive knowledge-base of human genes and genetic disorders. It consists of full-text overviews of genes and genetic phenotypes. In April 2003, the Human Genome Project led to sequence mapping of the whole human genome at a cost of approximately $2.7 billion. Since 2009, the rate of gene discovery for rare diseases has exponentially increased due to ‘next generation sequencing’, a new technology that has allowed us to sequence RNA and DNA much more quickly and cheaply.

It is expected that the genetic causes of almost all remaining conditions will be elucidated within the next few years. This knowledge will improve patient care and counselling for specific genetic conditions and will help our understanding of multiple DNA variants of more common conditions.

PHARMACOGENOMICS
This term refers to the advancement of personalised medicine, whereby drug therapy for an individual person is decided in light of his or her genotype, to ensure maximum efficacy with minimal adverse effects. We can now better categorise certain malignancies by examining the genomic changes in an individual tumour tissue rather than by the anatomical origins of that tumour. It is hoped that this clarity of genetic knowledge will lead to targeted management of the condition. There has already been real success applying the principle of gene therapy in some forms of genetic blindness, and hopefully this will be extrapolated to many other genetic conditions in the future.

THE 100,000 GENOMES PROJECT
This exciting UK development was announced by the Prime Minister in December 2012, and is being led by Genomics England (funded by the National Institute for Health Research to the tune of £300 million; www.genomicsengland.co.uk). The aim of the project is to sequence 100,000 genomes from approximately 30,000 patients with specific diseases. The project is due to go live in January 2015. The three categories of disease the project is concentrating on are rare diseases, cancer and infectious diseases. By sequencing these genomes we hope to be able to discover more genes involved with these diseases and understand how they interact. The aim is that this will lead to more personal and effective care for patients as well as providing great fuel for further academic research.

THE FUTURE
It is not inconceivable that patients may one day be able to visit clinicians with their own ‘genomic printout’, these data might provide a route to individualised therapy. Clearly a genomic printout for all raises many ethical, legal and social concerns, and is something of a minefield. Nevertheless the ‘genomisation’ of medicine is inescapable and here to stay, and is likely to give rise to remarkable opportunities for the future of clinical medicine and endocrinology.

WRITTEN BY PRADEEP VASUDEVAN
PHARMACOGENOMICS
This term refers to the advancement of personalised medicine, whereby drug therapy for an individual person is decided in light of his or her genotype, to ensure maximum efficacy with minimal adverse effects. We can now better categorise certain malignancies by examining the genomic changes in an individual tumour tissue rather than by the anatomical origins of that tumour. It is hoped that this clarity of genetic knowledge will lead to targeted management of the condition. There has already been real success applying the principle of gene therapy in some forms of genetic blindness, and hopefully this will be extrapolated to many other genetic conditions in the future.

THE 100,000 GENOMES PROJECT
This exciting UK development was announced by the Prime Minister in December 2012, and is being led by Genomics England (funded by the National Institute for Health Research to the tune of £300 million; www.genomicsengland.co.uk). The aim of the project is to sequence 100,000 genomes from approximately 30,000 patients with specific diseases. The project is due to go live in January 2015. The three categories of disease the project is concentrating on are rare diseases, cancer and infectious diseases. By sequencing these genomes we hope to be able to discover more genes involved with these diseases and understand how they interact. The aim is that this will lead to more personal and effective care for patients as well as providing great fuel for further academic research.

THE FUTURE
It is not inconceivable that patients may one day be able to visit clinicians with their own ‘genomic printout’, these data might provide a route to individualised therapy. Clearly a genomic printout for all raises many ethical, legal and social concerns, and is something of a minefield. Nevertheless the ‘genomisation’ of medicine is inescapable and here to stay, and is likely to give rise to remarkable opportunities for the future of clinical medicine and endocrinology.

PRADEEP VASUDEVAN
Consultant Clinical Geneticist, Leicester Royal Infirmary
Genetic technology is advancing so quickly that ethics is having a hard time catching up. The clearest example of the problem is knowing whether to test someone with an incurable disease and no family history. We desperately need consensus on the best approach to take. One way forward might be to understand how genes lead to disease.

‘Each of us carries a package of risk factors, some of which we are born with, and others we accumulate through life.’

**FAMILY SIZE AND SPORADIC DISEASE**

Genes show a property called penetrance. Penetrance is the probability of a disease manifesting given that you are carrying the disease mutation. It is easy to show mathematically that, even for mutations with quite high penetrance, unless you have a large number of siblings in your own and preceding generations, it is very possible that you will be the only person known to have been affected. In other words, Mendelian disease genes are expected to cause sporadic disease.

Now take a situation where there are ten offspring: 97% of such pedigrees will appear to show familial disease. But spontaneous mutation in the relevant gene is very unlikely. The second and more likely explanation is that, just by chance, the disease has not manifested in your family so far.
ALTERING THE GENOME: A DO-IT-YOURSELF GUIDE

WRITTEN BY ALIESHA GRIFFIN AND NILS KRONE

Traditional molecular biology often involves the study of genes outside their genomic context. However, over the past decade, major advances in the area of 'genome editing' have allowed for rapid, easy and efficient modification of endogenous genes in a range of cell types and animal models. These methods have been used to make targeted gene mutations and corrections, create specific gene knock-in and knock-out models, regulate gene transcription and visualise genomic loci.

The usefulness of gene editing has now extended directly into the medical field, as the first clinical applications are currently being explored. These novel technologies are fast becoming routine molecular biology techniques and will undoubtedly have a significant impact on medical research and disease treatments.

HOW DOES IT WORK?
To date, several different methods are available for gene editing. These include:

- zinc finger nucleases (ZFNs)
- transcription activator-like effector nucleases (TALENs)
- the recently developed clustered regulatory interspaced short palindromic repeat Cas9 nuclease (CRISPR/Cas9) system.

All methods rely on the same principle of introducing a double-stranded DNA break at a specific genomic location. In an effort to restore chromosomal integrity, these lesions are fixed via the cell's natural repair mechanisms, typically involving either non-homologous end joining (NHEJ) or homology directed repair (HDR) (Figure 1).

NHEJ involves the joining of the two chromosomal ends. However, this repair method is error prone and leads to the insertion or deletion of nucleotides which causes disruption of the protein-coding sequence. Alternatively, HDR uses recombination with an exogenously supplied template which contains a specific insertion or mutation. HDR has been used in a number of cell types and animal species to create the targeted insertion of functional elements including loxP recombination sites and fluorescent proteins. Additionally, HDR has been used to correct disease-causing point mutations in sickle cell disease and haemophilia B and is now being investigated for potential gene therapy applications.

ZINC FINGER NUCLEASES
ZFNs were one of the first widely available genomic engineering methods. They are built using zinc finger domains representing common DNA-binding motifs. These DNA-binding domains are fused to the FokI nuclease enzyme which creates the chromosomal breaks. Each zinc finger can be engineered to recognise a series of three nucleotides, and multiple zinc fingers are joined in tandem to target specific genome sequences. Since the FokI cleavage domain requires dimerisation for nuclease activity, two ZFNs are required to induce chromosomal breaks (Figure 2). This method was first successfully used in fruit flies more than a decade ago, and has recently been used in a small clinical trial to treat 12 people with HIV by specifically destroying a gene in their own derived immune cells.

TRANSCRIPTION ACTIVATOR-LIKE EFFECTOR NUCLEASES
TALENs consist of the DNA-binding 'TALE' linked to the FokI nuclease DNA-cutting domain. TALEs are composed of repeating modules that specifically recognise individual nucleotides. By changing the sequence of these modules, TALEs can be designed to target any desired gene sequence. As the TALE is fused to the FokI nuclease, TALENs, like ZFNs, must also be used as a pair to generate chromosomal breaks (Figure 2). Generation of TALENs for molecular biology purposes has become easily accessible to researchers by use of several commercially available kits, allowing laboratories to assemble customised TALENs more quickly and cheaply than ZFNs.

CRISPR/Cas9 SYSTEM
CRISPRs and the CRISPR-associated Cas9 nuclease function together as part of the adaptive immune system in bacteria. For genome-editing purposes, the Cas9, which cuts the DNA, is directed to the target sequence by a short guide RNA. By modifying 20 nucleotides within the target sequence, CRISPR/Cas9 technology can be used to induce double-stranded breaks in DNA, allowing for efficient and precise genome editing.

FIGURE 1. Genome editing relies on generating double-stranded DNA breaks which are repaired by the error prone non-homologous end joining or homology directed repair.
guide RNA, the Cas9 can be directed to specific chromosomal locations (Figure 2). In 2013, the CRISPR/Cas9 system was used to edit genes in mammalian cells and has since been developed and implemented by many laboratories in a range of applications. In the past 2 years, use of the CRISPR/Cas9 methodology has accelerated due to its simplicity, efficiency and cost-effectiveness compared with other methods, often making it the system of choice for research applications.

**WHICH METHOD IS BEST?**

ZFNs, TALENs and CRISPRs all have unique advantages and limitations which should be considered in the application and interpretation of genome engineering studies (Table 1). One major concern is the generation of off-target mutations within the cell, causing unwarranted genomic disruption. Despite efforts to predict and identify the off-target effects of these systems, no conclusive guidelines have yet been established. From a practical standpoint, CRISPRs are easier to implement than TALENs or ZFNs. TALENs and ZFNs must be constructed individually through timely assembly of the individual modules. In comparison, CRISPRs require the exchange of the 20 nucleotide sequence of the guide RNA. This can be simply ordered as a pair of oligonucleotides. The CRISPR/Cas9 system is suggested to be more effective in targeting the genome in comparison with ZFNs and TALENs. However, such comparisons require systematic analysis and will only be truly reflective as these methods become optimised.

**TABLE 1. COMPARISON OF GENOME EDITING TECHNIQUES**

<table>
<thead>
<tr>
<th></th>
<th>ZFNs</th>
<th>TALENs</th>
<th>CRISPR/Cas9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-target</td>
<td>Potentially more than TALENs</td>
<td>Fewer observed than CRISPR/Cas9</td>
<td>Potentially more than TALENs and ZFNs</td>
</tr>
<tr>
<td>Assembly</td>
<td>Labour intensive and rarely used</td>
<td>Several kits available, labour intensive</td>
<td>Easy and efficient</td>
</tr>
<tr>
<td>Target</td>
<td>Each zinc finger recognises 3 base pairs Not all 3-base pair combinations can be targeted</td>
<td>Each TALE module recognises a single base pair Target sequences are preceded by a thymine (T) residue</td>
<td>Needs a 3 nucleotide PAM (protospacer adjacent motif) sequence Up to five sequences can be targeted at once</td>
</tr>
<tr>
<td>Research</td>
<td>Genome editing Genetic regulation</td>
<td>Genome editing Genetic regulation</td>
<td>Genome editing Genetic regulation Imaging of genomic loci</td>
</tr>
<tr>
<td>applications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>Gene editing in T cells of HIV patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>applications</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 2.** Genomic editing methods rely on recognising specific DNA sequences and causing chromosomal breaks. (Details of individual methodologies are included in the text.)

Genome-editing technologies, such as ZFNs, TALENs and CRISPR/Cas9, have emerged to facilitate biomedical research through targeted gene modifications. Their easy assembly and accessibility have led to an exciting new era in scientific research which is capable of transforming basic biology, biotechnology and medical fields. These methods are still in their infancy, and more comprehensive studies are needed to determine their relative advantages in different experimental circumstances. However, with continual improvement, there are a host of new and exciting possibilities for both research and clinical applications.

**REFERENCES**

When considering DNA sequencing, I am often reminded of the 1990s TV programme *The X Files*, where, in the course of investigating some unexplained phenomenon, the entire genomic sequence from whatever weird organism that was worrying them that week would be immediately available. However, when lead characters Mulder and Scully were doing their sequencing, they would have done it ‘old school’, using radioactivity and X-ray film and, even by Hollywood standards, the suggested timescales were wholly fanciful. But, 20 years later, with the advent of high-throughput sequencing technologies, this apparent science fiction is now firmly rooted in reality.

**OLD SCHOOL SANGER SEQUENCING**

It was in the 1970s that Frederick Sanger developed a method for DNA sequencing that is still widely used today. Sanger describes the use of modified nucleotides where the 3-hydroxyl group needed for DNA elongation was replaced with a hydrogen atom. These ‘dideoxynucleotides’, when incorporated by DNA polymerase into a DNA strand, would then terminate elongation, as they were functionally unable to react with an incoming nucleotide.

Mixing proportions of the four native deoxynucleotides with their respective dideoxynucleotides yields a collection of nucleotide-specific terminated fragments, were radioactively labelled, but this evolved to a format that allows hundreds of millions to billions of polonies to be sequenced each time, hence producing enormous datasets of gigabases of DNA.

Originally the dideoxynucleotides, and therefore the size-separated terminated fragments, were radioactively labelled, but this evolved to a system based on fluorescence (Figure 1). It was at great cost (about $20 billion), and using this ‘Sanger’ sequencing method, that the human genome project was completed. The development of DNA sequencing garnered Fred Sanger his second Nobel prize.

**NEXT GENERATION OR BUST**

In 2006, an ‘X-prize’ was launched, offering $10 million to the first person or company to achieve 100 human genomes at less than $10,000 per genome. However, such was the speed of technical advance that this challenge was deemed NOT challenging enough and had to be cancelled.

The technical leap which introduced this next generation (probably best called ‘NOW generation’) sequencing was born of a change in philosophy. The old school method involved a specific known fragment of DNA to prime your sequencing reaction; thus you had to know a lot about what you were sequencing. All next generation sequencing technologies rely on sequencing random fragments, but in massively parallel fashion.

The DNA to be sequenced, which can range from a whole genome to much smaller segments, is made into a library of fragments to which synthetic DNA adapters have been covalently added. Using the universal sequences present on the DNA adapters, library fragments are amplified by polymerase chain reaction (PCR) on a solid surface that is coated with adapter sequences complementary to those that have been attached on the library fragments. This amplification results in a PCR colony, or ‘polony’, each originating from a single fragment of DNA.

In the massively parallel sequencing that follows, the process is a stepwise reaction series consisting of (a) a nucleotide addition step, (b) a detection step that determines the identity of the incorporated nucleotides on each polony of DNA that is being sequenced, and (c) a wash step that may include chemistry to remove fluorescent labels or blocking groups.

Figure 2 illustrates the method developed by Illumina, one of the major high-throughput sequencing platform providers. Thus, these high-throughput sequencing instruments conduct sequencing and detection simultaneously, rather than as distinct successive processes.

Critically, the parallel repurposing of spy satellite cameras, of the variety that was used to spy on Saddam Hussein’s swimming pool, meant that super high density images could be obtained on the scale of a sequencing machine. Thus these steps could now be performed in a format that allows hundreds of millions to billions of polonies to be sequenced each time, hence producing enormous datasets of gigabases per run.

**‘BUILD IT, THEY WILL COME’**

The initial driving force behind the development of next generation sequencing platforms was the sequencing of genomes. However, the interpretation of data emerging from whole genomes proved far more complicated than initially thought. Notably, as the technology matured and the cost inevitably dropped, the community began to adapt high-
throughput sequencing for use in a dizzying array of applications. These now include measurement of global gene expression, interrogation of transcription factor binding sites, sequencing of whole exomes, and even prenatal testing by sequencing small fragments of fetal DNA present in maternal blood. The cost still continues to drop, and the machines get smaller and more efficient. Although data storage and the required bioinformatics expertise to handle such data have now become the most significant bottlenecks, these are, in truth, readily surmountable.

The true power of this technology is currently only limited by the human imagination. To paraphrase the words of Kevin Costner’s character in *Field of Dreams*, ‘If you build it, they will come.’

GILES SH YEO
Wellcome Trust–MRC Institute of Metabolic Science, Addenbrooke’s Hospital, Cambridge

Giles Yeo is a molecular geneticist interested in understanding the mechanisms underlying the central control of food intake and body weight. Twitter: @GilesYeo.
GWAS: THE GREATEST HITS

WRITTEN BY ELEANOR WHEELER

For the last 8 years, scientific journals have been flooded with the ‘GWAS’ – or genome-wide association study. But what exactly is a GWAS?

Single nucleotide polymorphisms (SNPs, pronounced ‘snips’) are small variations in our DNA, where one base is substituted for another. SNPs are the most common type of genetic variation, occurring about once every 300 base pairs on average, and act as a map of markers across the genome. The idea behind a GWAS is simple: compare the frequency of these markers across thousands of individuals to identify correlations (or ‘associations’) between the genetic variants and traits of interest or common disease.

Prior to the GWAS, researchers had limited success applying traditional approaches to studying inheritance patterns in families (linkage studies) or investigating their favourite ‘candidate genes’ in relatively small numbers of individuals. The completion of the human genome sequence in 2003 provided detailed maps of SNPs across the genome and the International HapMap Consortium (HapMap) determined the correlation structure between them. Together, these enabled the majority of common genetic variations to be investigated in an unbiased way using commercially designed platforms containing many thousands of ‘tagging’ SNPs. These allowed regions of the genome to be tagged using a subset of variants that captured the information about a much larger set of correlated variants. Technological advances meant that these SNPs could be genotyped (assayed) in large collections of individuals from population and case-control studies.

USING GWAS TO MAKE ASSOCIATIONS

The GWAS ‘recipe’ has become fairly standard. Critical to its success are a well defined phenotype, clear analysis plan and stringent quality control criteria. Reference populations such as HapMap or the 1,000 Genomes Project, and the HapMap Reference Consortium (www.haplotype-reference-consortium.org), are used to estimate (‘impute’) the genotypes of untyped SNPs (those not captured by the genotyping array) based on the directly typed SNP genotypes. Each directly genotyped or imputed variant is then tested for association with the trait of interest, often taking forward the most promising signals to a validation stage in an independent sample of individuals. Empirical estimation of 1 million independent tests across the genome and the International HapMap Consortium (HapMap) determined the correlation structure between them. Together, these enabled the majority of common genetic variations to be investigated in an unbiased way using commercially designed platforms containing many thousands of ‘tagging’ SNPs. These allowed regions of the genome to be tagged using a subset of variants that captured the information about a much larger set of correlated variants. Technological advances meant that these SNPs could be genotyped (assayed) in large collections of individuals from population and case-control studies.

Imputation to a common set of SNPs also enables researchers to increase sample sizes by combining summary level data in a meta-analysis, and large international consortia such as the Meta-Analyses of Glucose and Insulin-related Traits Consortium (MAGIC; www.magicinvestigators.org) have been hugely successful using this approach.

Plots can be used to investigate the quality of the data and association results. Manhattan plots (named as they resemble the Manhattan skyline) show each variant with its genomic location along the x-axis and the negative logarithm of the association P value (so that the most interesting SNPs appear at the top of the plot) on the y-axis. The majority of the points should show no association, with clusters of SNPs forming ‘peaks’ around association signals.

DATA – EXPLAINING THE UNEXPECTED?

The GWAS has transformed the landscape of complex trait genetics research and (as of August 2014) the National Human Genome Research Institute (NHGRI) Catalogue includes 1,961 scientific publications and 14,012 genetic variants associated with a wide range of phenotypes. Despite all the reported associations, in most cases, the genetic component of a given trait explained by GWAS is much smaller than we would expect based on estimates from family and twin studies.

There is much debate on the reason for this so-called ‘missing heritability’, and some argue that the GWAS approach has been unsuccessful for complex traits. However, fully explaining disease risk is not essential to provide insight into disease, and examples such as the complement pathway for age-related macular degeneration and the role of autophagy in Crohn’s disease show where the GWAS has been successful at highlighting the molecular pathways underlying disease, providing potential targets for therapy. For example, over 50 variants have been identified related to body mass index (BMI), but cumulatively, they explain less than 2% of the proportion of inter-individual differences in BMI that are estimated to be due to genetic factors, far less than expected (40-70%).

LOOKING TO THE FUTURE

The technique will continue to be the method of choice for many studies while it remains cost-effective compared with sequencing. However, there is now a clear emphasis not only on finding new variants, but also on increasing our understanding of the underlying biological pathways and processes. In particular, there is a focus on fine-mapping the associated regions to identify the causal genetic variants underlying the signals, alongside novel methods to prioritise signals by incorporating biological and genomic features.

REFERENCES

3. The 1,000 Genomes Project Consortium 2010 Nature 467 1061–1073.

ELEANOR WHEELER
Senior Staff Scientist,
Wellcome Trust Sanger Institute, Cambridge

Eleanor Wheeler works as a statistical geneticist, using large scale datasets including SNP array data and next generation sequence data to identify genes involved in metabolic diseases and related quantitative traits.

12 | THE ENDOCRINOLIGIST | WINTER 2014/15
A long-acting somatostatin analogue therapy, uniquely formulated and providing effective treatment of acromegaly and the symptoms of neuroendocrine tumours

START RIGHT & STAY RIGHT

Somatuline Autogel is a unique nanotube formulation that allows therapy to start right with a rapid therapeutic response...1,2

…and stay right through sustained, long-term control;2-4 it is conveniently administered from ready-to-use syringes with an automatic safety system.

References:

For more information on Somatuline Autogel, please contact: Ipsen UK Medical Information Department 190 Bath Road, Slough, Berkshire SL1 3XE.
Tel: 01753 627777.
Email: medical.information.uk@ipsen.com
Website: www.ipsen.co.uk/somatuline
UK/02000935 Date of preparation: August 2012.
Genetics and geneticists have an ever-increasing role in the endocrine clinic. But how can you benefit best from this fast-moving discipline – and what do you need to know? We asked leading experts for their opinions.

**GENETICS: AN EXCITING NEW TOOL WITH EXCITING NEW ETHICS**

Management of patients with endocrine disorders has traditionally relied on detailed clinical assessment, supported by increasingly accurate hormone assays. However, the genetic element of endocrine disease is increasingly reaching the clinical environment, as advances made in molecular biological research are translated into practice.

Endocrine diseases range from complex disorders with multiple associated genetic loci (e.g. obesity, diabetes, autoimmune thyroid disease, hyperlipidaemia) that are influenced by environmental factors, to disorders associated with single gene disruptions (e.g. endocrine tumours, MEN1, RET, SDHB).

The precise molecular genetic basis of many inherited conditions has been elucidated over the past two decades, and contributes to the increasing referral of patients for genetic testing. Such investigation may:

- confirm the clinical diagnosis (e.g. MEN1 mutation in combined primary hyperparathyroidism, insulinoma and prolactinoma of multiple endocrine neoplasia type 1 (MEN1))
- identify affected and unaffected relatives to enable screening or reassurance respectively (e.g. RET mutation in MEN2)
- allow prenatal testing in pregnancy to prevent disease development (e.g. in utero treatment of affected female babies that have a 21-hydroxylase (CYP21A2) mutation of congenital adrenal hyperplasia for the prevention of virilisation)
- identify a relevant genetic cause by post-diagnostic testing in a rare disease (e.g. CDC73 mutation in parathyroid carcinoma).

However, any genetic investigation may have associated social, legal and ethical issues for which clinicians must be equipped prior to referral for testing.

**INCIDENTAL DISCOVERIES**

Analogous to the identification of incidentalomas with cross-sectional imaging studies, genetic testing may detect abnormalities that are beyond our current understanding, so that their interpretation is problematic. Genetic screening may reveal novel genetic sequence variants of known disease-causing genes that are either harmless polymorphisms or pathogenic mutations. Therefore, functional characterisation in a genetics research laboratory may be necessary to define the biological consequences.

**FINE-TUNING TREATMENT**

Consider the 40,000 people in the UK who have a monogenic diabetes. Some patients (30%) may have a glucokinase (GCK) mutation that causes maturity-onset diabetes of the young (MODY), characterised by mild hyperglycaemia and requiring no treatment. Other patients with a hepatocyte nuclear factor 1 homeobox A (HNF1A) mutation (50%) have MODY that is often misdiagnosed as type 1 diabetes and treated with insulin, but patients actually respond best to low dose sulphonylurea treatment instead, due to the underlying molecular mechanism of pathogenicity. Therefore, genetic testing can be vital to obtain the correct diagnosis and provide optimal clinical management.

**THE VALUE OF VIGILANCE**

Furthermore, a clinical role has developed for the surveillance and management of asymptomatic patients who carry a pathogenic mutation, such as in MEN syndromes. They need regular screening investigations and may require planned prophylactic interventions. One successful example can be found in MEN2 patients who inherit RET mutations, where medullary thyroid carcinoma can be prevented by thyroidectomy, from as early as 6 months of age.

However, if the window of opportunity to eliminate C cell disease is missed in these patients, the prospect of cure falls from 95% to less than 30% if lymph node metastases present before treatment (and to less than 4% if more than 10 involved lymph nodes are present).

Management is assisted by clinical practice guidelines in families with inherited endocrine disease, such as in MEN1 syndrome, with a requirement for regular biochemical and cross-sectional imaging for the early detection of endocrine tumours. However, it is important to remember that detailed clinical assessment is of primary importance in the clinical management of patients, with molecular genetics contributing secondary support.

**MORAL DILEMMAS**

Thus, genetic testing is an established part of clinical endocrine practice and provides an opportunity to enhance patient management and optimise outcomes. However, novel issues in the areas of consent, confidentiality and privacy emerge when results are relevant to biologically related relatives. For example, incidental non-paternity can be detected in diagnostic testing for disease, with challenging repercussions.

In clinical practice, we need to recognise the growing role of genetic investigation and may need support from continuing professional development training programmes to address the ethical, legal and social dilemmas that can be raised by the results of molecular diagnostics.

Steven Alexander Wright, an American comedian, has remarked that ‘the problem with the gene pool is that there is no lifeguard’! Perhaps we are called to be prepared for such endocrine genetic rescues, as we strive to manage endocrine disease in the modern genetic era.

**REFERENCES**

WHAT IS THE ROLE OF A CLINICAL GENETICIST IN ENDOCRINOLOGY?

The last three decades have seen an exponential increase in the number of genetic tests available to practicing clinicians. In the future, the Department of Health envisages that more and more genetic testing will be ‘mainstreamed’, with non-geneticists requesting most of the diagnostic tests. The Clinical Genetics service will continue to see patients with dysmorphic syndromes and multi-system disorders, advise on prenatal diagnosis and pre-implantation genetic diagnosis and counsel on predictive testing. They will also provide help with interpretation of genetic variants of uncertain clinical significance. So, as endocrinologists, how do we now familiarise ourselves with the issues surrounding genetic testing?

WHO SHOULD HAVE A GENETIC TEST?
If a reliable, cost-effective genetic test is available and the test result would make a significant change to the management of a patient or family, it would be reasonable to offer it. The genetic testing process should start with an affected member of the family in the first instance.

UNDERSTANDING TEST METHODOLOGY
Sanger sequencing has been the mainstay of molecular genetic testing for decades; however, an increasing number of genetic tests now employ next generation sequencing (see page 10). This approach has the advantage of testing a number of different genes at the same time with reduced cost per gene and more rapid turnaround of results. The laboratory may report results from a selected number of genes (a panel test) or the whole exome/genome. Panel-based tests are currently available for clinically well defined genetically heterogeneous disorders such as the hereditary phaeochromocytoma/paraganglioma syndrome (see page 16).

Larger deletions and duplications are missed by sequencing unless a quantitative approach or another technique such as MLPA (multiplex ligation-dependent probe amplification) is used. Also, sequencing may miss certain types of genetic changes, such as triplet repeat disorders and mosaicism. Next generation sequencing-based panels are clearly an improvement on Sanger sequencing. However, when several genes are tested at the same time, there is a greater likelihood of finding variants of uncertain clinical significance. There are also ethical issues surrounding incidental findings and storage and retrieval of data in relation to exome-/genome-based testing.

PHENOTYPING
Reliable phenotyping of patients would continue to be of great importance. With most endocrine disorders, this is done by endocrinologists rather than geneticists. The suggested ‘mainstreaming’ would mean that endocrinologists will need to familiarise themselves with referring patients for genetic testing, so saving an appointment with the geneticist and ensuring a faster turnaround of result. It follows that the gate-keeping role, currently done by the geneticist, would pass on to the endocrinologist. UKGTN (UK Genetic Testing Network) provides guidelines regarding indications for genetic testing.

PRE-SYMPOMATIC TESTING
If tests identify a disease-causing genetic change, a genetic counsellor can do subsequent cascade pre-symptomatic testing of the family. This differs from a diagnostic test; factors such as the age of the patient, natural history of the disease, options available to the patient and implications for insurance have to be considered.

DEALING WITH UNCERTAINTY
The human genome has thousands of variants, most of which are benign. Some of these may have been reported in association with disease, but may not always be disease-causing. The first confirmation of a variant as disease-causing requires extra diligence. As a rule, variants of uncertain clinical significance should not be used for predictive testing, prenatal diagnosis or pre-implantation genetic diagnosis.

Family studies may help to assess if a variant has arisen anew or tracks with the disease in the family. Genetics units, used to doing such tests, could come in at this point. This would also mean closer co-operation between endocrinologists and geneticists and may include joint/parallel clinics and multidisciplinary meetings.

We have to accept that a genetic test may not always yield a black and white result. Sometimes, we may not be able to classify a variant as disease-causing or otherwise on the basis of the available evidence, in which case, reviewing the results after 2 or 3 years may be helpful.

Different mutations in the same gene may have varying phenotypic effects. The genotype-phenotype correlations are important in diseases such as MEN2 and congenital adrenal hyperplasia. Some of the conditions we believe to be monogenic may be modified by other genetic or environmental factors.

WHERE TO SEND THE SAMPLE?
The NHS Regional Genetics laboratories are currently undergoing a process of reorganisation with the aim of reducing the number of laboratories and rationalising testing. The diagnostic tests available through the NHS laboratories are advertised by UKGTN and their own websites. This usually includes the cost and turnaround times.

Diagnostic tests for some rarer disorders may not be available through UKGTN laboratories. When requesting a genetic test through a private laboratory, either in the UK or abroad (see EDDNAL, Genetests), it is important to check for quality assurance, cost and turnaround times. Genetic tests are offered as part of research projects as well. These have less stringent quality control; their turnaround times are usually much longer and results are not always guaranteed. It is good clinical practice to confirm the results in an accredited diagnostic laboratory wherever possible.

THE FUTURE
Molecular genetics is advancing at a very rapid pace. The training most clinicians have received in genetics is limited. This calls for continuing education for all clinicians, including geneticists. The Wellcome Trust holds courses on genomic medicine for clinicians periodically at their Cambridge site, and more such courses are likely to be available to non-geneticists in the near future.

The genomic era in medicine is still in its early days, but undergoing rapid growth. As genetics and genomics become a greater part of medical education and clinical practice, this calls for closer co-operation between geneticists and endocrinologists.

AJITH KUMAR AND MÁRTA KORBONITS
Ajith Kumar is a Consultant in Clinical Genetics at Great Ormond Street Hospital, London. Márta Korbonits is Professor of Endocrinology at Barts and the London School of Medicine, Queen Mary University of London.
In 1886, Felix Frankel published the first article describing a case of phaeochromocytoma (PH). Two years previously, an 18-year-old woman with a history of paroxysmal palpitations, headaches and reduced visual acuity had died and, on autopsy, was found to have bilateral adrenal tumours.

Further cases were reported and attempts at surgical removal of the tumours met with some success, but it was not until 1937 that Edwin Beer and colleagues were able to prove that adrenaline was the pressor substance behind the hypertensive crises. Familial PH was first mentioned in the literature in 1947, by which time bilateral cases and extra-adrenal paragangliomas (PGLs) had also been reported.

PGLs and PHs are neuroendocrine tumours arising from the adrenal medulla and autonomic ganglia respectively. They are rare, with an estimated incidence of 1 in 300,000. Tumours arising from parasympathetic paraganglia, which are mainly located in the head and neck, cause symptoms by their pressure effects on local structures. Only 5% of these secrete catecholamines, compared with sympathetic tumours (which include PHs), where it is closer to 90%. All these tumours can also be asymptomatic, as evidenced by their higher incidence at autopsy.

**GENES AND TESTING**

Despite their rarity, understanding of the genetics of hereditary PGLs/PHs has exploded in recent years. The tidy and memorable ‘rule of 10s’ is no longer applicable. Rather than 10% being inherited, studies have shown that around 35% of PGL/PH cases harbour a causative germline mutation, a very acceptable hit rate to justify genetic testing. Indeed, some would say that genetic testing should be offered in all cases of PGL/PH.

There are currently 13 known genes associated with PGLs/PHs. To allow clinicians to navigate the genetic territory efficiently, gene-testing algorithms are regularly updated to reflect increasing knowledge of genotype-phenotype correlations. Well known syndromes associated with PGLs/PHs, such as Von-Hippel Lindau (VHL), multiple endocrine neoplasia type 2 (RET gene) and neurofibromatosis type 1 (NF1 gene) display autosomal dominant inheritance, and individuals with a family history or a clinical phenotype in PGL/PH genes and the development of more effective therapies.

**THE ROLE OF IMPRINTING**

Dominant inheritance patterns tend to be the norm. Mutations in the SDH, SDHA and SDHB genes also show a parent-of-origin effect. They are maternally ‘imprinted’, which means that children are only at risk of developing tumours if they inherit the mutation from their father. For example, a woman with a PGL due to a SDHD mutation has a 50% chance of passing the mutation to each of her children, but none would be affected. However, if her son passed the mutation to his children, they would be at risk of developing tumours (see Figure). Therefore, it could take three or more generations to accumulate a family history of multiple affected individuals, which illustrates the importance of genetic testing in apparently sporadic cases.

**MOSAICISM AND MULTIPLE PGLS**

HIF2A is a newly recognised gene involved in PGLs/PHs. Inherited mutations in this gene cause congenital polycythaemia. Recent publications have described individuals with polycythaemia and multiple PGLs who are mosaic for an HIF2A mutation. Mosaicism is the presence of two different cell lines in an individual. For the same HIF2A mutation to be present in multiple tumours, the mutational event will have occurred very early in development. Depending on the level of mosaicism it may be detectable in the blood or other tissues, but this is not guaranteed. This also begs the question of whether a proportion of the germ cells harbour the mutation, which would pose a risk to future children that cannot be quantified, even with new testing techniques.

**LOOKING TO FUTURE THERAPIES**

The benefits of genetic testing in cases of PGL/PH are similar to other inherited cancer syndromes. It may provide prognostic information for the proband and guide management and future screening decisions. If a mutation is identified, cascade testing for relatives can identify those who are genuinely at risk and require screening. However, screening can only attempt to detect tumours early. Hopefully, in the future we will see a greater understanding of the relationship between genotype and phenotype in PGL/PH genes and the development of more effective therapies.

VANI JAIN AND ALEXANDRA MURRAY

University Hospital of Wales, Cardiff

Vani Jain is an ST4 and Alexandra Murray a Consultant in Clinical Genetics.
ENDOCRINOLOGY: ‘SINE STERCORE TAURI’

WRITTEN BY SHLOMO MELMED

Endocrinology, like all of US academic medicine, is currently beset by a perfect storm of decreased clinical reimbursement, and sharply decreased funding for research and training, accompanied by an increased physician and scientist administrative burden.

Practice patterns have changed, with more centralised guideline requirements, accountable quality controls and insistence on transparent outcome metrics. Striving for value (both quality and cost) are high imperatives for our professional activities. Nevertheless, instead of writing this column about the already well described challenge of maintaining our scholarly discovery while facing an existential fiscal cliff, I choose to comment on another pervasive threat facing US endocrinology today.

Writing in the *The New Yorker* in 2005, Holt analysed the ‘cultural and conceptual assault’ on the truth which pervades society in general, and academia in particular. Accordingly, the title of this piece (literally ‘Endocrinology without the excrement of the bull’) is paraphrased from a paper by GA Cohen, the Oxford political philosopher, who lamented the ‘indifference to meaning’ displayed by the ‘b.s.’ of academicians.

In his 1988 presidential address to the American Society of Clinical Investigation, Nobel Laureate Robert Lefkowitz, of G protein-coupled receptor fame, distinguished the falsity of lying from the fakery of b.s.¹ In fact, the purveying of academic b.s., which has little regard for either truth or falsehood, is an ongoing threat to our profession. I am sure that we can all cite instances where endocrinologists are perceived to disregard truth and corrupt the scientific process which is based on ‘the founding of conclusions based on accurate and appropriate data’.

Two egregious examples of such ubiquitous professional b.s. in our field come to mind: the shameful exploitation and administration of hormone replacement for reversing the ageing process, and the over-diagnosis of adrenocorticotrophin-secreting pituitary microadenomas in patients with commonly encountered pseudo-Cushingoid features.

In addition to the patient harm and unnecessary cost engendered by unfounded therapies or procedures, these examples of endocrine b.s. are in fact indifferent to the truth. The liar, by contrast, understands the truth and chooses to deviate from it.

‘These enterprises are not based on true falsehoods, but rather on a devious manipulation of scientific truths.’

Thus, the random isolated finding of a low serum insulin-like growth factor-I level in an 80-year-old patient is used to justify costly, unproven and inappropriate growth hormone replacement to reverse or slow the ageing process, with all its attendant side effects. The ‘anti-ageing’ industry is thriving, with fully equipped sophisticated clinics offering comprehensive endocrine evaluations and therapies for those with the means to pay. These enterprises are not based on true falsehoods, but rather on a devious manipulation of scientific truths. Similarly, the obesity epidemic has resulted in a plethora of available endocrine evaluations dedicated to discover a ‘hormonal’ cause for the corpulent patient. Thus, the surgical resection of an incidental pituitary microadenoma in an obese, hirsute, hypertensive patient with type 2 diabetes without a rigorous biochemical diagnosis is reflective of an indifference to scientific evidence. Availability of expensive imaging and endocrine testing for diagnosing Cushing’s disease in obese subjects is advertised on the web, often with local hotels recommended for out of town patients. These patients usually yearn for a diagnosis, yet results of these costly endocrine evaluations often lead to a fake ‘Cushing’s’ label, followed by recommendation of an unnecessary surgical procedure.

Both these misrepresentations of scientific facts by endocrinologists are disguised as truths by ‘improvisation, colour and imaginative play’, in the words of Princeton philosopher Harry Frankfurt. Hence coining of the term ‘b.s. artist’ is understood in this light. Most importantly, in addition to the perversion of truth by this pseudo-endocrine science, countless patients are exposed to the endocrine b.s. purveyed by physicians whose motives and self-delusion both exceed their knowledge and understanding of the scientific facts used to purvey the b.s.

‘We are responsible to society for maintaining our own unflinching professional standards, and erosion of our values will lead to loss of public confidence and support which we rightly enjoy.’

Lefkowitz is correctly disheartened that the b.s. artists in our midst, by obfuscation or hyperbole, are greater enemies of the truth than liars. Accordingly, appropriate measures already in place to maintain scientific integrity and uncover plagiarism or data falsification are not effective in unmasking endocrine b.s.

Our discipline of endocrinology is shamed by such adept fakery by practitioners. We are responsible to society for maintaining our own unflinching professional standards, and erosion of our values will lead to loss of public confidence and support which we rightly enjoy. We are therefore spurred to educate our trainees in the rigorous pursuit of scientific truth, as well as to inform them of the principles of scientific integrity, and recognition of the quackery masquerade of the endocrine b.s. artist.

REFERENCES

FROM THE CHIEF EXECUTIVE’S DESK:
NEW APPROACH, SAME PRINCIPLES

WRITTEN BY LEON HEWARD-MILLS

Learned societies exist to promote a (scientific) discipline and to encourage excellence. As a charity, our Society is more than a membership organisation. It has a responsibility to advance and promote scientific and clinical education and research in endocrinology for the public benefit.

Whether devised at a college meeting or coffee shop, or, like our own Society, conceived on a bus to Croydon, the common theme among learned societies large and small is a thirst for knowledge: sharing experience, validating research and improving standards.

This has been the case for over 300 years. The principles and outputs are effectively the same now as they were when members of the (then nameless) Royal Society first met in London in the 1660s: to discuss scientific ideas of the day in a collegiate atmosphere and disseminate peer reviewed scientific discoveries through meetings and journals. This dissemination was done using the ground-breaking technology of the day and produced a standard that has worked well for 400 years. Look at an article from Philosophical Transactions of 1814 and it is not that dissimilar to an article of 2014.

This is why I welcome the new learning initiatives announced on page 28 of this issue for the Society’s official clinical journal, Clinical Endocrinology. Online education using the latest technologies will ensure that science is not only disseminated, but that complex technical principles are understood. Our Society will soon launch journal-based learning modules across Journal of Endocrinology, Journal of Molecular Endocrinology and Endocrine-Related Cancer, ensuring that all Society journals offer a comprehensive online learning service. We will bring you more information on this shortly. This will be followed with a series of clinical modules across the specialty during 2015.

In my view, education through digital platforms will never replace good collegiate face-to-face meetings. During 2015, our Society will be promoting short, focused science meetings to complement activities at the SfE BES conference. These will be low cost, high quality events with an emphasis on specialist cutting-edge science. More on this will follow in future issues of The Endocrinologist.

However, it is online learning that provides our greatest opportunities to reach the highest number of members, scientists and clinicians, with validated, relevant, trusted fundamental and breakthrough content. This will allow us to remain true to the original ideals of our Society and prove valuable and accessible to future generations of endocrinologists.

LEON HEWARD-MILLS
Chief Executive, Society for Endocrinology, and Managing Director, Bioscientifica Ltd
Email: leon.heward-mills@endocrinology.org

Visions of endocrinology photography competition

What does endocrinology mean to you? We are looking for a collection of images that encapsulates the diversity of the discipline, tells our stories, and reflects the huge range of people working in endocrinology.

› Scientific/medical
› Clinical practice
› Research environments

Five winning images will be chosen by our panel of judges. These images, together with five runner-up images will be displayed at SfE BES 2015 and be featured in The Endocrinologist and as part of other Society materials.

INDIVIDUALS WHO SUBMIT THE WINNING IMAGES WILL EACH WIN A £100 PHOTOGRAPHY VOUCHER.

Email your high resolution images to media@endocrinology.org by Tuesday 23 December 2014.

Individuals may submit up to three images of which they must be the sole copyright owner.

Please see www.endocrinology.org for full terms and conditions.
HOO K, LINE AND THINKER
FROM OUR SCIENCE COMMITTEE CORRESPONDENT

Anyone who has ever compiled a programme for a symposium, written a review or been asked for editorial comment on someone’s cool new data will be familiar with the tricky task of getting a good title. There is, it seems, an increasing need for a little verbal eye candy to draw in an audience.

If done with style and wit, this is a wholly positive thing. Just like a well wrapped present, it is immediately attractive and cheering, raising the spirits in anticipation of good things to come. It suggests the authors have taken care over their output, and may have a world view beyond the end of the bench.

Take the story of five professors in Sweden’s Karolinska Institute who have been entertaining themselves and their readers by sneaking Bob Dylan lyrics into their writing on nitric oxide and neuronal development – whoever includes the most before they retire wins lunch at the local restaurant.

I do worry though that this lyrical playfulness might be lost on some of their target audience. Ask most people under 25 about Blonde on Blonde and they’re unlikely to recognise it as a classic double album from 1966.

My own attempts to drop in cultural hooks from popular music have often fallen flat. Chuck Berry doing his ‘duck walk’ (illustrating the drive of testosterone), The Smith’s ‘Some girls are bigger than others’ (the inherited nature of body composition) and Groove Armada’s ‘If everybody looked the same’ (the role of hormones in physical appearance) have all led to blank stares.

But this was nothing in comparison to the echoing silence a close colleague received when illustrating a talk on cardiac arrhythmias with the ‘...Speed it up...Slow it down...’ line from the 1981 Eurovision entry by Bucks Fizz. (Younger readers: use an image-based search engine, and please accept my apologies; those were simpler times.)

My colleague decided she urgently needed to ‘get down with the kids’ and came across The Mindset List. Compiled by two emeritus professors at Beloit College in Wisconsin, USA (www.beloit.edu/mindset), it’s a telling reminder that many cultural reference points are incredibly transient. Wire-rimmed glasses mean ‘Potter’ not ‘Lennon’; water coolers are where you fill your water bottle, not a social meeting spot. It’s time to think up some new tag lines because, like Bob says, ‘You’d better start swimmin’ or you’ll sink like a stone’.

TONY COLL
Science Committee correspondent

YOU NEED TO NETWORK!
FROM OUR CLINICAL COMMITTEE CORRESPONDENT

Recognising a need for a dedicated forum within each major area in endocrinology, your Society recently launched the blueprint for new Endocrine Networks. As you may have read in the Spring issue of The Endocrinologist, the first Endocrine Network (in reproductive development; work on patient engagement and information; and

WHAT ARE THE BENEFITS?
Networks will create a new structure for networking and sharing ideas and opportunities for you, the Society’s members. The aim is to promote collaboration both within the Society and with other organisations.

As practice within endocrinology increases in sub-specialisation, the Clinical Committee recognises the value to you of belonging to networks that facilitate clinical and scientific information sharing, including liaison with other interested bodies. Endocrine Networks provide excellent platforms for you to share experience and ideas regarding the organisation and delivery of clinical services, particularly in the context of specialist commissioning.

Additionally, Endocrine Networks will provide suggestions for the SfE BES conferences, identifying the most appropriate topics and speakers. They may also make proposals for areas of guideline development; work on patient engagement and information; and

FIND OUT MORE AT WWW.ENDOCRINOLOGY.ORG/ENDOCRINENETWORKS

contribute to clinical audit and endocrine research – networks will facilitate the gathering of pilot data to then apply for funding from external organisations.

HOW DOES IT WORK?
Each Endocrine Network will provide an effective voice and community so that experts, trainees and interested parties can interact regularly using electronic media, local meetings, etc.

The Society will provide a central fund, for which networks will be able to bid by means of a simple application. The Society’s Sponsored Seminar Grant may also be used to support activities.

Endocrine Networks will be organised, formal structures, led by two Network Leads appointed for 3 years. Each network will provide an annual report outlining current and proposed activity.

The successful establishment of Endocrine Networks depends on the enthusiasm and commitment of you, the members. Please discuss these opportunities with colleagues, and consider how you might get involved!

PAUL CARROLL
on behalf of the Clinical Committee
With hundreds of tickets sold, and prominent coverage in the country’s top newspapers, your Society has had its most successful season of public events so far. Following our previous success at science festivals, we decided to break out of our comfort zone and take endocrinology somewhere less expected – a music festival!

Teaming up with the Society of Biology and the Royal Veterinary College, we set up a science stall at the increasingly popular Green Man Festival near Brecon. We had one simple aim: to engage the public with the role of hormones in sexual attraction and mating rituals.

It was hard to miss our stall, appropriately billed ‘The Love Zoo’, as it was a converted mobile library parked at the entrance to one of the festival’s busiest thoroughfares. Our audience was large and diverse – families looking for a break, students recovering from last night’s antics and wide-eyed children who had heard rumours about a gigantic tarantula.

Without a doubt, our most talked-about activity was ‘Groom a Gorilla’, where a member of the public would ‘groom’ a member of our staff dressed in a gorilla suit by removing parasites stuck to their fur while simultaneously learning about the role of oxytocin in mammalian bonding.

During less busy periods, we ran impromptu sing-a-longs about the role of reproductive hormones in the animal kingdom.

So how did it go? Well, you know it’s been a successful event when, without a hint of embarrassment, a group of young adults sing with you about reproductive hormones at the top of their lungs! Truly a magical music festival experience.

OMAR JAMSHED
Communications Assistant, Society for Endocrinology
MAKING SENSE OF ENDOCRINE DISRUPTORS

Endocrine disruptors are making headlines. Do these ubiquitous substances, found in our environment, food and consumer products pose a health threat? The Society for Endocrinology has teamed up with Sense about Science (SAS) and the British Society for Paediatric Endocrinology and Diabetes (BSPED) to provide guidance on what we know so far, and clarify whether the public is getting accurate information about the health implications posed by these chemicals.

To the trained eye, headlines like ‘Gender-bender chemicals “putting everyone at risk”’ will automatically trigger a healthy dose of scepticism. But for the general layman, who may not have the knowledge or time to dig deeper, these headlines can have a powerful impact and may genuinely cause worry.

A recent article in The Daily Mail headlined ‘Fertility time bomb found in drinking water’ claimed that ‘the fertility of a generation of men is being put at risk because a hormone found in the Pill is getting into drinking water’. The article did not take into account that city river water contains more waste water and so tends to contain larger quantities of oestrogen and other hormones compared with rural areas. The higher level of hormones is due to the higher concentration of people who are excreting hormones in their urine – a small proportion of which is oestrogen and progesterone from the contraceptive pill. When this water is processed for drinking water, active endocrine chemicals are almost entirely removed, leaving only trace amounts. Oestrogens remaining in tap water after processing are well below the level that could cause an effect and would be far outweighed in concentration by any oestrogens you might consume from a glass of milk or a steak. Not providing these facts to the public amounts to scaremongering and erodes trust in science and scientists.

The booklet which is being produced by Sense About Science in collaboration with the Society for Endocrinology and BSPED is called Making Sense of Endocrine Disruptors. It is one in a series of booklets from SAS which aim to present the science and dispel myths around research that has commonly been misconstrued by the media.

The guide will also explore many other issues, such as why scientific studies that show no effect are not as widely reported in the media as those that do. It is often the case that a new study with results demonstrating an adverse health effect will be reported widely, but if subsequent studies find these initial dramatic findings to be flawed, they are much less likely to be covered. From simple concepts like understanding that correlation does not imply causation, to more complex problems like the relationship between endocrine disruptors and non-monotonic dose responses, the guide will leave no stone unturned when addressing this hugely topical issue.

Available shortly, the guide will be promoted to journalists and the public and made available on the Society website and at www.senseaboutscience.org.

REFERENCES
1. Lean G Mail Online http://dailym.ai/1ox01eB.

BNA FESTIVAL OF NEUROSCIENCE 2015

The British Neuroscience Association (BNA) Festival of Neuroscience 2015 is taking place in Edinburgh, UK on 12–15 April 2015. The Festival will highlight some of the best international research into the brain and nervous system, and will bring together speakers and delegates from many different disciplines. The Society for Endocrinology is sponsoring a session entitled ‘Sleep, circadian rhythms and the neuroendocrine system’ with prestigious speakers including Hugh Piggins (Manchester), Margriet Westerterp (Maastricht, The Netherlands), Eve Van Cauter (Chicago, IL, USA) and Jonathan Johnston (Guildford).

For more details, see www.bna2015.org. The early bird registration deadline is 6 January 2015.

REMEMBER TO RENEW!

Society membership for 2015 commences on 1 January. If you have already set up a direct debit arrangement there is no need to do anything as your membership will automatically be renewed.

However, if you don’t yet have a direct debit subscription, call the Membership Team today on +44 (0)1454 642253 or email members@endocrinology.org to renew your membership.

To find out more about the benefits of joining the Society for Endocrinology, visit www.endocrinology.org/membership.
WELCOME TO 2015!
YOUR SOCIETY EVENT AND GRANT PLANNER

IT’S TIME TO CHANGE YOUR DIARY...

Endocrine Nurse Update

16–17 March 2015
Birmingham

Clinical Update

16–18 March 2015
Birmingham

SfE BES 2015

2–4 November 2015
Edinburgh

2015 will see exciting changes to the usual Society event calendar. The Society for Endocrinology BES conference is set to move to November from its former spring timeslot, while Clinical Update and Endocrine Nurse Update will take place in March rather than in the autumn.

CAN WE HELP YOU GET THERE?

Would you like to present your work at an endocrine meeting but need financial support to get there? As a Society member, you could be eligible for a Conference Grant of up to £500 (or up to £850 for an overseas meeting) each year.

CONFERENCE GRANT DEADLINES ARE CHANGING FOR 2015!

Note these new deadlines for your grant applications, corresponding to the Society’s new events calendar:

15 December 2014
Grant applications for Society for Endocrinology Endocrine Nurse Update, the US Endocrine Society conference, and all other overseas meetings ending before 15 March

15 March 2015
Grant applications for overseas meetings ending before 15 July

15 July 2015
Grant applications for the Society for Endocrinology BES conference plus any other overseas meetings ending before 15 December

Find out more, including revised eligibility criteria, at www.endocrinology.org/grants

FREE PLACES at SfE BES 2015

Open to Student Members as well as non-members who have yet to choose endocrinology as their specialty

Candidates must be nominated by a Full Member of the Society

See www.endocrinology.org/grants

‘My Society for Endocrinology Conference Grant helped to fund a trip to the American Endocrine Society meeting in the States; this provided me with a great opportunity to present some of my research findings to an international audience.’

Get the latest Society meeting information at www.endocrinology.org/meetings
A NEW GRANT FOR THE NEW YEAR?

Your membership of the Society for Endocrinology opens the door to a wide range of grants and educational opportunities, many of which can support you through the early part of your career.

**EARLY CAREER GRANTS**
Up to £10,000 per grant
Supporting early career endocrinologists with funding for research resources to help further their career. Apply by 27 May or 27 November.

**PRACTICAL SKILLS GRANTS**
Up to £2,000 per grant
Helping Scientist-in-Training and Associate Members to visit labs to learn a technique, carry out experiments essential to their projects, or attend lab-based workshops to gain practical skills. Apply year-round.

**CLINICAL DEPARTMENT VISIT GRANTS**
Up to £2,000 per grant
Enabling Clinician-in-Training Members to visit clinical departments other than those within their rotation, to see endocrinology practised in a different setting. Apply year-round.

**SUMMER STUDENTSHIPS**
£185 per week for up to 10 weeks, plus up to £1,000 for consumables.
Allowing undergraduate students to gain experience in a research environment. Apply by 11 March.

**SPONSORED SEMINAR GRANTS**
Up to £3,000 per grant
Supporting members wishing to host one-off endocrine seminars to raise awareness of endocrinology as a discipline and attract scientists, clinicians and nurses into the specialty. Apply year-round.

**PUBLIC ENGAGEMENT GRANTS**
Up to £1,000 per grant
Enabling members to organise outreach activities, aimed at school children and/or the general public, to communicate the science of endocrinology. Apply year-round.

Leading the way in endocrine education, research and support
www.endocrinology.org/grants

‘The first author on the paper which has just been accepted for publication was one of my MRes students (who was awarded a free place at the SfE BES conference). It was my first last author publication, so this helped me to secure a permanent academic position – I’m now a lecturer. I’m very grateful to the Society for their support over the years and I hope I can give something back in the future.’

EARLY CAREER GRANT RECIPIENT

‘I was awarded a Summer Studentship which not only helped me to enhance my supervision and teaching skills, but also provided a superb research project for an undergraduate student who was able to present her findings at the SfE BES conference.’

SUMMER STUDENTSHIP RECIPIENT
Welcome to our new column providing information and career support to those starting out in endocrinology and their mentors.

‘From a certain point onward there is no longer any turning back. That is the point that must be reached.’

FRANK KAFKA (FROM THE TRIAL, 1925)

Where do endocrinologists come from? This is a question that currently vexes the higher echelons of UK endocrinology, as they contemplate the same recruitment crisis that currently besets almost all the medical specialties. Much of the focus is on how to overcome the stigma attached to a specialty which remains yoked to the acute medical take.

An alternative way to tackle this issue is to ask instead ‘How do you make an endocrinologist?’ and acknowledge that there are a great many undifferentiated student and trainee doctors who are waiting for the signals to turn themselves into hormone doctors. There are trainees who emerged from the womb as fully fledged orthopaedic surgeons, but there are many more ‘pre-pro-endocrinologists’ who would be receptive to a nudge towards our discipline. It behoves those of us who are a little further along this pathway to catalyse the process.

A NUDGE IN THE RIGHT DIRECTION

In an ideal world, a description of your own personal favourite feedback loop to the students on the ward round would suffice. However, instead suggest to them that they start an endocrine student society. There will be money available to help in the medical school, and you can be the guest of honour at their first meeting, where your preferred homeostasis analogy will get a wider audience.

In addition, remind them that membership of the Society for Endocrinology is free for students, and comes with all sorts of perks. CVs will be adorned on all sides to sweeten the deal, and a path of least resistance towards the hormonal life will start to emerge.

For good or ill, Modernising Medical Careers assembled a roadblock preventing the emerging endocrinologist from being waved through onto the professorial firm. Encourage those in the first year of foundation training (FY1s) on other teams to organise a taster week with your firm.

Create an expectation within the firm that everyone should have an interesting case to take to the national and local Clinical Cases meetings and other conferences. Make it a key role of the registrar to help them turn this into a case report, a format that is currently undergoing a renaissance. Watch in wonder as the case report author helps you with that book chapter.

Meanwhile, the Academic Foundation Programme has a significant number of members who don’t really know what they’re going to do with a 4-month break from the wards. Make the effort to find out who they are, show an interest in them and install them into your nearest laboratory or clinical study group.

An NUDGE IN THE RIGHT DIRECTION

In an ideal world, a description of your own personal favourite feedback loop to the students on the ward round would suffice. However, instead suggest to them that they start an endocrine student society. There will be money available to help in the medical school, and you can be the guest of honour at their first meeting, where your preferred homeostasis analogy will get a wider audience.

In addition, remind them that membership of the Society for Endocrinology is free for students, and comes with all sorts of perks. CVs will be adorned on all sides to sweeten the deal, and a path of least resistance towards the hormonal life will start to emerge.

For good or ill, Modernising Medical Careers assembled a roadblock preventing the emerging endocrinologist from being waved through onto the professorial firm. Encourage those in the first year of foundation training (FY1s) on other teams to organise a taster week with your firm.

Create an expectation within the firm that everyone should have an interesting case to take to the national and local Clinical Cases meetings and other conferences. Make it a key role of the registrar to help them turn this into a case report, a format that is currently undergoing a renaissance. Watch in wonder as the case report author helps you with that book chapter.

Meanwhile, the Academic Foundation Programme has a significant number of members who don’t really know what they’re going to do with a 4-month break from the wards. Make the effort to find out who they are, show an interest in them and install them into your nearest laboratory or clinical study group.

If you have an idea for a topic you would like to see covered in this section, please contact us at endocrinologist@endocrinology.org.
**WHAT’S STOPPING YOU?**
**HOW AN EARLY CAREER GRANT CAN CHANGE YOUR LIFE...**

**EARLY CAREER GRANTS**, from the Society for Endocrinology, can help you to further your career in many ways, up to 10 years post-PhD, by:
- Providing resources to finalise a project or gain preliminary data
- Funding a piece of equipment
- Short term financing of a salary

On your behalf, we asked recipients of the 2010 and 2012 Early Career Grants what the grant had helped them achieve. As you can see, the results are quite impressive.

**WHERE ARE THEY NOW?**

**2 YEARS ON**
Grant recipients of 2012

<table>
<thead>
<tr>
<th>Total Society for Endocrinology Early Career Grants Awarded</th>
<th>£247,285</th>
<th>£196,100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still Members of the Society</td>
<td>87%</td>
<td>76%</td>
</tr>
<tr>
<td>Have Since Moved Institution</td>
<td>13%</td>
<td>24%</td>
</tr>
<tr>
<td>Total External Funding Received Since Their Early Career Grants</td>
<td>£1.1 m</td>
<td>£4.1 m</td>
</tr>
</tbody>
</table>

**4 YEARS ON**
Grant recipients of 2010

<table>
<thead>
<tr>
<th>Total Number of Endocrine Papers They Have Published Since Receiving Their Awards</th>
<th>30 by 17 of the 23 individuals, an average of 1.8 articles each</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have Since Gained a More Senior Position</td>
<td>5%</td>
</tr>
<tr>
<td>Have Since Moved Institution</td>
<td>13%</td>
</tr>
<tr>
<td>Total Number of Endocrine Papers They Have Published Since Receiving Their Awards</td>
<td>136 by 21 individuals, an average of 6.5 articles each</td>
</tr>
</tbody>
</table>

**WOULD YOU LIKE THE SOCIETY TO INVEST IN YOUR FUTURE?**

Apply for an Early Career Grant or you might miss out!

The next deadline is **27 May 2015**, then every November and May.

Apply online via [www.endocrinology.org/grants/grant_earlycareer.html](http://www.endocrinology.org/grants/grant_earlycareer.html).

**The Early Career Grant has enabled me to successfully begin my research project in polycystic ovary syndrome. It has provided me with important pilot data for further grant applications and enabled me to collect data for my research MD and develop future projects in this field.**

**ANDREW LANSDOWN, CARDIFF**

**The award allowed me to further the aims of my fellowship and to offer a number of MRes student projects. This invaluable experience as lead supervisor has resulted in a number of conference presentations and awards for my students.**

**KAREN FORBES, MANCHESTER**

**The grant has helped me start to establish independent projects and collaborations, and contributed to work for a publication that is currently in submission.**

**KIM JONAS, LONDON**
I was delighted to receive the Annette Louise Seal Memorial Award from the Addison’s Disease Self Help Group during the Society for Endocrinology BES conference 2014 in Liverpool. This award is made for an abstract in the ‘Nursing Practice’ category which advances the clinical management of adrenal insufficiency, where the first author is a nurse. My abstract was entitled ‘Steroid group education: developing a curriculum ensures good nursing practice is maintained’.

In Portsmouth, we have a long-standing tradition of using group education sessions for patients with diabetes. These have been recognised as a successful way of enhancing self management skills. So, when I started steroid education for endocrine patients, I decided to use the same format.

**REACHING EVERY PATIENT**

Eight years ago, when I first taught patients how to administer emergency steroid injections, I needed to educate every relevant patient in the district because, prior to my initiative, patients were not routinely given an emergency injection kit. We knew most relevant patients within the endocrine department; but I also wrote to all local GPs and asked them to pass on an invitation letter to any of their patients on steroid replacement therapy. I hoped this would ensure we contacted everyone who might benefit.

With a local population in excess of 600,000, this meant I had many patients in need of education. Weekly groups were set up, each with up to six patients and their relatives. The group met for an hour and I used the same format each time. The first 50 patients were asked to evaluate their experience and the outcomes were positive. Once all existing patients had the opportunity to attend it was possible to reduce the frequency of the groups.

**WORKING WITH COLLEAGUES**

A few years later I was fortunate to be joined by Sarah, who is a trained diabetes educator. I wanted to share running the steroid education groups with her, so she observed me conducting some groups. It became clear that, to ensure we both used the same format, we needed a curriculum. Once written, this included step by step details to conduct a group (Box 1) with relevant educator behaviours (Box 2).

**ENSURING CONSISTENT PATIENT SUPPORT**

Developing a curriculum has advantages for patients as they receive the same education whichever nurse runs their group session. The ‘take home’ messages are consistent and, if we later take a call from a patient who has been to a group, we can be confident of the information they have been given. The curriculum is also an important part of succession planning, because at some point over the next few years our endocrine nurse team will change, and it is important that this successful education programme continues.

I am a great believer in using group education for steroid-dependent patients. The group scenario gives the patient a richer experience than individual patient education can. Even when groups include patients with a variety of formal educational abilities, you find they learn from each other’s self management experiences.

I am happy to share the curriculum with other endocrine nurses who are establishing steroid education groups. A copy can be obtained by emailing me at jean.munday@porthosp.nhs.uk.

---

**BOX 1. Curriculum content**

1. Prepare room and documentation
2. Outline basic anatomy and physiology of endocrine system with reference to reasons why steroid replacement is required
3. Talk about doses, timing of medication during everyday life, and how that differs if someone is unwell
4. Discuss what to do when unable to tolerate oral steroids, urgency of need for injected hydrocortisone
5. Teach participants how to inject hydrocortisone
6. Ensure they understand need to seek urgent medical advice
7. Discuss travel requirements
8. Mention patient support groups

**BOX 2. Educator behaviours**

- Ask open questions
- Ask ‘focused’ questions
- Open questions to the group and ‘fill in the gaps’ where necessary
- Facilitate of group discussion
- Reflect statements back to individuals and the group
- Use minimal encouragers
- Support silence

---

Congratulations to Jean from all at the Society for recently being shortlisted for Nurse of the Year by the Nursing Times Awards.
With the festive celebrations only just around the corner, it does not seem long since I saw you at the Endocrine Nurse Update (ENU) in Birmingham. The conference was well received and the feedback excellent. It was also encouraging to see lots of endocrine nurses attending for the first time. ENU takes on an exciting new format next year. Your feedback is important in developing future meetings, so do pass on any suggestions to events@endocrinology.org.

On a celebratory note, Jean Munday has written here about her excellent work which led to her receiving the Annette Louise Seal Memorial Award from the Addison’s Disease Self Help Group (ADSHG) during the Society for Endocrinology BES conference 2014. This was awarded for her abstract ‘Steroid group education: developing a curriculum ensures good nursing practice is maintained’. We thank her for her article, which I am sure many of you will find interesting.

Not only was Jean given an award by ADSHG this year, she was also shortlisted for ‘Nurse of the Year’ in the Nursing Times Awards. This emphasises the valuable work undertaken by endocrine specialist nurses, not just for their organisations, but also for their patients. Endocrine nurses perform a wide range of specialist tasks and can make a huge difference to patients’ experiences and treatment. Whilst we may be few in number compared with other nursing specialties, it highlights the importance of our role and raises the profile of endocrine nursing.

As you know, we all need to work to raise awareness of endocrinology nursing, so please share your experiences, successes or practice with us by emailing endocrinologist@endocrinology.org. We are always pleased to hear from you and to include your news in future issues.

Finally, just before you go and enjoy the festivities, I hope you will join me in thanking our retiring Nurse Committee members, Ann Marland (Oxford) and Morag Middleton (Aberdeen), for all their hard work and support during the past 4 years.

LISA SHEPHERD
NURSE COMMITTEE CHAIR

17TH ANNUAL CLINICOPATHOLOGICAL CONFERENCE ON PITUITARY DISEASE

This conference, focusing on a multidisciplinary approach to pituitary disease, is taking place on 2 February 2015 at the Royal College of Obstetricians and Gynaecologists in London. Keynote speakers include Tony Goldstone and Andy Toogood. To register, visit www.cfsevents.co.uk/clinico.html, or for more information, contact conference organiser Stephanie Baldeweg at stephanie.baldeweg@uclh.nhs.uk.

GRAHAM BULL PRIZE

Applications may now be made for the Royal College of Physicians’ Graham Bull prize in clinical science. This prize of £1,000 is offered to a researcher under the age of 45 who has made a major contribution to clinical science.

Applications close on 30 March 2015 and further details can be found at http://bit.ly/1vT1sCG.

£20,000 BTF RESEARCH AWARD

The British Thyroid Foundation (BTF) offers an annual award to support 1-year research projects into thyroid function or thyroid disorders. This year’s award of up to £20,000 is specifically for research into assaying and assessment of thyroid function with particular application to the diagnosis and management of hypothyroidism. The award can be used to supplement existing projects or to help get research ideas started. Funds will be awarded for consumables, running costs and equipment.

The BTF is a National Institute for Health Research (NIHR) partner organisation in respect of its research award funding stream. Studies funded through this funding stream are eligible for inclusion in the NIHR Clinical Research Network Portfolio and are therefore able to access NHS support via the NIHR Clinical Research Network infrastructure.

For further information and an application form, visit www.btf-thyroid.org, email research-award@btf-thyroid.org or phone +44 (0)1423 709707. The closing date for receipt of applications is 31 January 2015.

SOCIETY FOR ENDOCRINOLOGY CORPORA T SUPPORTERS 2014

Platinum Supporter: Bioscientifica Ltd
Gold Supporters: Ipsen Ltd Novartis Pharmaceuticals UK Ltd ViroPharma
Silver Supporters: HRA Pharma Internis Lilly Pfizer Ltd Sandoz Biopharmaceuticals

For more information, visit www.endocrinology.org/corporate or contact amanda.helm@endocrinology.org.
Whatever your stage of training or your level of experience, you should take advantage of this exciting new educational resource brought to you by Clinical Endocrinology, the Society for Endocrinology’s official clinical journal.

CONTINUING MEDICAL EDUCATION

This free e-learning programme provides continuing education activities online. Modules, based on articles published in Clinical Endocrinology, are specifically designed to match the major training curricula in the UK and Australia. They include simple take home messages and revision material to place the article in perspective.

Multiple choice questions, based on the information contained in the module, use the same format as materials provided by the Royal College of Physicians and the Royal Australasian College of Physicians. They are set at the same standard and include notes explaining the correct (and incorrect) answers. A formal certificate of completion is supplied with each module to enhance your ePortfolio. You can digitally store completed activities and retrieve your certificates whenever you need them.

BUT WAIT – THAT’S NOT ALL

You will also be able to amaze and impress your colleagues and friends with your knowledge derived from a historical perspective (not examinable, but educational, nonetheless). You can discover original descriptions of classic endocrine disorders and the important historical figures who described them, as well as learning about famous historical figures who suffered from endocrine conditions.

The modules are written and are reviewed by experts in the field to enhance the value of articles published in Clinical Endocrinology, to assist trainees with their education and to provide a resource for more experienced clinicians requiring material for continuing professional development. The modules are ideal for study groups or ‘journal club’ presentations.

The resource has been developed with assistance from the Clinical Endocrinology Trust, using technology provided by CECity: the platform that powers Continuing Medical Education, Healthcare Improvement and Maintenance of Certification programmes for over 2 million health professionals worldwide.

NOTHING TO PAY, AND NO ADVERTS!

Just go to the website www.wileyhealthlearning.com/een to register and start using the modules.

STEPHEN JUDD
Senior Editor (Education), Clinical Endocrinology
DAVID R HADDEN
(1936–2014)

WRITTEN BY BREW ATKINSON AND PATRICK BELL

David Hadden, a long-time member of the Society for Endocrinology, died at his home in Belfast on 26 February. He was an internationally recognised expert on growth, nutrition and diabetes.

Anticipating the impact of the westernised lifestyle on the epidemic of type 2 diabetes, in 1972, David set up the Belfast Diet Study, which confirmed that strict adherence to diet alters the course of the disease. Subsequently, his collaborative work in the UK Prospective Diabetes Study demonstrated for the first time the importance of good control of blood glucose in preventing the complications of type 2 diabetes.

His other great contribution was to the management of diabetic pregnancy. The joint diabetes obstetric service he built up with his colleagues the late Graham Harley and Desmond Montgomery was an example copied nationally. He made his native Belfast a major centre and central laboratory in the multinational Hyperglycaemia and Adverse Pregnancy Outcome Study, which highlighted the potentially adverse effects of small increases in blood sugar in the non-diabetic mother – findings that continue to challenge and change practice.

David was proud of being part of a well known Irish medical family. As a family doctor in Skibbereen, County Cork, his great-grandfather treated many victims of the Irish potato famine. Many years later, David’s grandfather was working as a ship’s doctor on an ocean liner bound for Liverpool from New York when it ran aground near Ballycastle. This chance event led to him settling in Portadown, Northern Ireland, where David was born and grew up across the road from the practice run by his grandfather, father and aunt. David graduated with honours from Queen’s University Belfast in 1959.

His early training in endocrinology and diabetes began in his beloved Royal Victoria Hospital, Belfast. After a Clinical Research Fellowship using the new technique of radioimmunoassay to measure growth hormone, he travelled as a Fulbright Fellow to the Johns Hopkins Hospital, Baltimore, MD, USA. His identification there of a growth hormone binding protein was published in Nature. Although this novel finding was dismissed by conventional thinking at the time, his paper is now recognised as one of the first descriptions of that important regulatory protein.

His work on growth and nutrition continued at the Department of Experimental Medicine in Cambridge, under the supervision of Professor RA McCance, and as an MRC Fellow at the Malnutrition Research Unit in Kampala, Uganda. There his work elucidated the differing mechanisms of kwashiorkor and marasmus.

He was appointed Consultant Physician to the Metabolic Unit (now the Regional Centre for Endocrinology and Diabetes) at the Royal Victoria Hospital in 1967, and worked there until his retirement in 2001. He brought his interest in growth back to Belfast where children were beginning to be treated using growth hormone extracts. The experience in malnutrition was used to develop his ideas on the treatment of type 2 diabetes, at least in part a disease of excessive nutrition.

As a physician he was very caring and regarded himself as permanently on-call. The pressure colleagues experienced as a result of his attention to detail and determination to get things right, and his somewhat quizzical manner, was balanced by his friendliness and his own personal commitment. His clinical work and research covered the full range of endocrinology and diabetes.

His work and qualities were marked by an Honorary Chair at Queen’s University Belfast and numerous lectureships including the 1997 Jørgen Pedersen Lecture of the Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes, the 2006 Norbert Freinkel Award of the American Diabetes Association and, in 2012, the first Lifetime Achievement Award of the Irish Endocrine Society.

Locally he is remembered by generations of Belfast medical students who, for over 25 years, attended his Saturday morning case demonstrations. This commitment summed up his desire to help and support colleagues.

Of many interests outside medicine, perhaps the most memorable was his own millennium project to produce Irish linen, possibly inspired by his mother’s family, the Johnstons, who had been involved in the linen industry. He started by growing and harvesting the flax at his country cottage and then succeeded, with some difficulty, in arranging for the whole process of retting, spinning and weaving to be performed in Ireland. As foreign competition had undermined this once thriving industry, authentic Irish linen had not been manufactured locally for many years. David handled the news of a terminal diagnosis with characteristic dignity, declined the offer of chemotherapy and proceeded to carry on as best he could. He was still writing and attending lectures until a few days before his death. He is survived by his wife Diana, a doctor and artist, son Robert, a neurologist, and daughters Katharine and Emily. He will be greatly missed by his colleagues throughout the world.

BREW ATKINSON

PATRICK BELL
AVERTING A CRISIS: 30 YEARS OF SUPPORT FOR PEOPLE WITH ADDISON’S
WRITTEN BY KATHERINE WHITE

The Addison’s Disease Self Help Group (ADSHG) celebrated its 30th anniversary in autumn 2014. In 1984, newly diagnosed Deana Kenward, a mother to two young boys at the time, sat down at her kitchen table and wrote, by hand, to the 80 people who had responded to her ‘advert’ in The Radio Times. We believe this makes the ADSHG the first endocrine support group established anywhere in Europe.

Deana’s motivation was simply to meet others with the same rare condition, and to overcome her loneliness and worries. One early member recalls that ‘I used to drop everything to read her typed letters – they were so welcome because I knew of no-one else with the problem.’ In 2012, Deana Kenward was awarded an MBE for her 28 years of dedicated service to the ADSHG; she is still very much involved in maintaining the Group.

DEFINING A PURPOSE
The internet age radically enlarged the capabilities of the ADSHG, but its core purpose and values remain the same: sharing experiences in managing steroid dependence, in a group run by and for people with Addison’s disease. Isolation is less of a challenge than it used to be, for a condition affecting perhaps 8,500 people scattered across the UK, or 140 per million. However, most Group social meetings welcome newcomers who are encountering others with Addison’s for the first time – in some cases up to 40 years after their diagnosis.

PROVIDING CRUCIAL SUPPLIES
In spring 2014, the ADSHG began distributing injection kits through its web shop, containing Vanishpoint syringes, disposable amp snaps and photo instructions for use of the retracting, integrated safety needles. These are proving popular; nearly one-third of the group’s 1,400+ members purchased a kit in the first 6 months after the launch. The amp snaps overcome many of the problems with glass cuts and shattered vials that are typically reported by inexperienced patients and their families.

EMBRACING TECHNOLOGY
Thanks to an IT-savvy trustee, Nick Willson, the ADSHG was an early adopter of web technology. Its website was created in 2000. The Group’s first formal print publication, the Owner’s Manual, was the first free PDF. The ADSHG continues to make all its medical publications available as free PDF downloads, at www.addisons.org.uk/publications.

A web-based private members’ discussion forum, created in 2008, was the next major IT development for the group. The most widely read topic, running from 2011 onwards and viewed 1,738 times, has been about ambulance registration for priority response to a 999 callout.

The Facebook age has seen rival web forums multiply over recent years, both commercial start-ups such as Health Unlocked and privately run chat-sites. However, the ADSHG trustees recognise that British culture tends to be reticent about medical conditions and that not everyone is a ‘joiner’. For those who simply want to browse the web, without subscribing to a support group for the additional member benefits of meetings and a newsletter, the ADSHG now makes printed information kits available through its web shop. The ADSHG itself was a reluctant, late entrant to Facebook, and in early 2014 launched a page (www.facebook.com/addisons.org.uk) signposting the Group’s actual website.

A CHARITABLE VENTURE
Ten years ago, the ADSHG was approved for charitable accreditation by the Charity Commission. By that time, the Group had an elected committee of trustees and an affiliated, independent panel of endocrine advisors chaired by Professor John Wass. However, operating on a shoestring of voluntary labour, the Group’s annual turnover at this milestone was still less than £5,000. In the 10 years since, its turnover has multiplied tenfold, to pass the £50,000 mark.

The ADSHG operates without office space or paid staff, relying on self-employed contractors – scattered from rural Gloucestershire to Lichfield and Penzance – for core functions in database management, print design, accountancy, stock warehousing and distribution for its web shop sales.

A STRATEGY FOR EMERGENCIES
In 2003, the newly formed executive committee had to set priorities for the group’s future direction. Emergency prevention and treatment swiftly emerged as the need that was felt most strongly around the table. Sarah Baker, the originator of the Owner’s Manual, suggested it might be a good aspiration to have injection practice at the Group’s future meetings. Over time, this became a reality.

Professor Mike Besser, the group’s first medical advisor, was one of the early medical speakers who obligingly rolled up his sleeves and demonstrated orange-stabbing, on a Saturday afternoon in the back hall of a Guildford pub. In more recent years, under the watchful eye of endocrine nurse Phillip Yeoh, attendees at the annual medical lecture in London have been motivated to practise on themselves, injecting saline into thigh and/or upper arm. Most are pleasantly surprised to discover how little it hurts, and thrilled at their achievement.

EMBRACING TECHNOLOGY
Thanks to an IT-savvy trustee, Nick Willson, the ADSHG was an early adopter of web technology. Its website was created in 2000. The Group’s first formal print publication, the Owner’s Manual, was the first free PDF. The ADSHG continues to make all its medical publications available as free PDF downloads, at www.addisons.org.uk/publications.

A web-based private members’ discussion forum, created in 2008, was the next major IT development for the group. The most widely read topic, running from 2011 onwards and viewed 1,738 times, has been about ambulance registration for priority response to a 999 callout.

The Facebook age has seen rival web forums multiply over recent years, both commercial start-ups such as Health Unlocked and privately run chat-sites. However, the ADSHG trustees recognise that British culture tends to be reticent about medical conditions and that not everyone is a ‘joiner’. For those who simply want to browse the web, without subscribing to a support group for the additional member benefits of meetings and a newsletter, the ADSHG now makes printed information kits available through its web shop. The ADSHG itself was a reluctant, late entrant to Facebook, and in early 2014 launched a page (www.facebook.com/addisons.org.uk) signposting the Group’s actual website.

A CHARITABLE VENTURE
Ten years ago, the ADSHG was approved for charitable accreditation by the Charity Commission. By that time, the Group had an elected committee of trustees and an affiliated, independent panel of endocrine advisors chaired by Professor John Wass. However, operating on a shoestring of voluntary labour, the Group’s annual turnover at this milestone was still less than £5,000. In the 10 years since, its turnover has multiplied tenfold, to pass the £50,000 mark.

The ADSHG operates without office space or paid staff, relying on self-employed contractors – scattered from rural Gloucestershire to Lichfield and Penzance – for core functions in database management, print design, accountancy, stock warehousing and distribution for its web shop sales.

A STRATEGY FOR EMERGENCIES
In 2003, the newly formed executive committee had to set priorities for the group’s future direction. Emergency prevention and treatment swiftly emerged as the need that was felt most strongly around the table. Sarah Baker, the originator of the Owner’s Manual, suggested it might be a good aspiration to have injection practice at the Group’s future meetings. Over time, this became a reality.

Professor Mike Besser, the group’s first medical advisor, was one of the early medical speakers who obligingly rolled up his sleeves and demonstrated orange-stabbing, on a Saturday afternoon in the back hall of a Guildford pub. In more recent years, under the watchful eye of endocrine nurse Phillip Yeoh, attendees at the annual medical lecture in London have been motivated to practise on themselves, injecting saline into thigh and/or upper arm. Most are pleasantly surprised to discover how little it hurts, and thrilled at their achievement.

PROVIDING CRUCIAL SUPPLIES
In spring 2014, the ADSHG began distributing injection kits through its web shop, containing Vanishpoint syringes, disposable amp snaps and photo instructions for use of the retracting, integrated safety needles. These are proving popular; nearly one-third of the group’s 1,400+ members purchased a kit in the first 6 months after the launch. The amp snaps overcome many of the problems with glass cuts and shattered vials that are typically reported by inexperienced patients and their families.

You can view the ADSHG’s complete medical information product range, which includes hospital ‘steroid alert’ stickers for the drugs chart, the emergency card, surgical guidelines, How to Avoid Precipitating an Adrenal Crisis and nursing leaflets at www.addisons.org.uk/shop.

KATHERINE WHITE
ADSHG Chair and Clinical Advisory Panel Co-ordinator

CONTACT DETAILS FOR PATIENTS
• Email: feedback@addisons.org.uk
• Web: www.addisons.org.uk
• Facebook: www.facebook.com/addisons.org.uk
• Postal address: ADSHG, PO Box 1083, Guildford GU1 9HX

LEFT: An informal social meeting hosted by trustee Jan Dryden at her home, with injection training led by A&E nurse Maria Green (with baby Elizabeth).
Here are the latest highlights from our journal Cover Art Competition, showcasing the best images in endocrinology.

**COVER IMAGE FROM JOURNAL OF MOLECULAR ENDOCRINOLOGY**
**AUGUST 2014**

The image depicts the tibial growth plate ultrastructure in 51-day-old female Sprague-Dawley rats. The sections are stained with Alcian Blue van Gieson. Credit: K Sundström, Karolinska University Hospital, Stockholm, Sweden

Enter our Cover Art Competition for Journal of Endocrinology, Journal of Molecular Endocrinology and Endocrine-Related Cancer.

Visit [www.endocrinology.org/news](http://www.endocrinology.org/news) for more information.
Tostran® (testosterone) 2% Gel Prescribing Information

Please refer to the Summary of Product Characteristics (SPC) before prescribing.

**Presentation**: Tostran 2% Gel, contains testosterone, 20 mg/g.

**Indication**: Replacement therapy with testosterone for male hypogonadism when testosterone deficiency has been confirmed by clinical symptoms and laboratory analyses.

**Dose**: The starting dose is 3 g gel (60 mg testosterone) applied once daily to clean, dry, intact skin, on the abdomen or to both inner thighs. Adjust dose according to clinical and laboratory responses. Do not exceed 4 g of gel (80 mg testosterone) daily. Apply after washing, bathing or showering. Do not apply to the genitals. Do not use in women, or children under the age of 18 years.

**Contraindications**: Known or suspected carcinoma of the breast or the prostate. Hypersensitivity to any of the ingredients.

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

**Interactions**: Androgens can increase the anticoagulant effect of anticoagulants. Concurrent administration with ACTH or corticosteroids may increase the likelihood of oedema.

**Side-effects**: Very common: application site reactions (including paresthesia, xerosis, pruritis, rash or erythema). Common: increased haemoglobin and haematocrit, increased male pattern hair distribution, hypertension, gynaecomastia, peripheral oedema, increased PSA. May cause irritation and dry skin. Consult SPC for further details of side-effects.

**Pack Size and Price**: Packs containing one or three 60 g metered-dose canisters per pack. Price £28.67 per canister.

**Legal Category**: POM.

**Marketing Authorisation Holder**: ProStrakan Limited, Galabank Business Park, Galashiels, TD1 1QH, UK. Marketing Authorisation Number: PL16508/0025


References:

Date of preparation: February 2014. Job code: MO15/1224

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