

THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

A HISTORY OF ENDOCRINOLOGY:

*the fantastical
world of
hormones*

THE
JOURNEY
TO MODERN
ENDOCRINOLOGY

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A WORD FROM THE EDITOR...



Welcome to this 'History of Endocrinology' themed edition, which has come together wonderfully well. We start with an introduction to the fantastical world of hormones, and then take a journey through the modern history of pituitary surgery. Following this, we learn about key discoveries in parathyroid, adrenal, thyroid and oestrogen- and testosterone-related endocrinology. I am very grateful for the time our big-hitting contributors have given up in order to write for us this time round.

One of the joys of *The Endocrinologist* magazine is that it allows us to look at over-arching themes in endocrinology and, in so doing, it brings us all together as an endocrine community.

Perhaps no publication related to the history of our discipline should omit mention of the name Victor Cornelius Medvei. This man's enthusiasm and passion for our subject led him to write the definitive textbook, *A History of Endocrinology*, during his retirement. A copy should be on every endocrinologist's bookshelf.

As clinicians and scientists or mere enthusiasts, we are all continually contributing to the progress of our subject, and thereby influencing its present and past. Who knows, some of you reading today's magazine may be responsible for major breakthroughs in our speciality, and feature in future historical accounts of endocrine discovery ... happy reading!

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www.endocrinology.org/endocrinologist

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

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

Deadline for news items for the Summer 2015 issue: **12 March 2015**.

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

Front cover image ©SHUTTERSTOCK



NEW FACES AT THE ENDOCRINOLOGIST



Rosemary Bland

We're delighted to welcome Rosemary Bland and Dominic Cavlan (London) as new members of the Editorial Board of *The Endocrinologist*. Our grateful thanks go to retiring members Karen Featherstone (Manchester) and Olympia Koulouri (Cambridge) for all their hard work and input over the last 2 years.

The Editorial Board aims to ensure the views and interests of all Society members are represented and included in *The Endocrinologist*. If you would like to contact the Editorial Board with ideas for articles, topics or your feedback, please email endocrinologist@endocrinology.org.



Dominic Cavlan

WHO'S A MEDAL WINNER IN YOUR FIELD?

Nominations are sought for the Society's 2016 Medals. The Dale, Transatlantic, Society, Starling, European and International Medals each honour individuals for their significant achievements in endocrinology. Only the Society and Starling Medals must be awarded to Society members; the others are open to any suitable nominees. The deadline for nominations is 31 July 2015. You can find full details and nomination forms at www.endocrinology.org/about/medals.html.

NOMINATIONS FOR NEXT PRESIDENT

Professor Sir Stephen O'Rahilly will retire as the Society's President at the 2016 AGM, so a President-elect is sought to commence their role in November 2015. Council's nominee for this post is Graham Williams (Imperial College London). If any member wishes to suggest an alternative, contact Julie Cragg in the Society office (julie.cragg@endocrinology.org) by 18 March 2015.

WITH REGRET

We were saddened to hear of the untimely death of Jenny Pell of the University of Cambridge. Jenny was an active and valued Society member. She served as Senior Editor for *Journal of Endocrinology* (2005–2011), on our Science Committee (until 2008) and as a faculty member at the Autumn Endocrine Retreat (now the Career Development Workshops). The Society extends its condolences to Jenny's family and friends. An obituary will appear in our next issue.

Look out for the brand new Society for Endocrinology blog, **THE ENDOCRINE POST!** endocrinologyblog.org

NEW COUNCIL AND COMMITTEE MEMBERS NEEDED

You are encouraged to nominate replacements for Jonathan Seckl, Tony Weetman and Anne White, who retire from the Society's Council in November 2015, having served their 4-year terms of office.

Vacancies on the Clinical, Early Career Steering Group, Finance, Nurse, Programme, Public Engagement and Science Committees will also arise at the end of 2015. If you would like to be involved in running your Society, please consider standing for election!

Details and nominations forms are on the specific committee pages at www.endocrinology.org/about/committee.html. The closing date is 31 July 2015.

SPECIAL ISSUES...

Don't forget that *Journal of Endocrinology* (JOE) and *Journal of Molecular Endocrinology* (JME), which are both Society journals, publish regular special issues looking back at the history of endocrine disorders. Recently, the 20th anniversary of leptin was marked in JOE, and 25 years of molecular endocrinology were commemorated in JME. Visit www.try-joe.org and www.try-jme.org for more information.



SfE BES 2014 SHORTLISTED FOR BEST CONFERENCE

The 2014 Society for Endocrinology BES conference has been shortlisted for yet another award! It is a finalist for 'Best Association Conference - Outside London' in the Association Excellence Awards 2015, which recognise best practice and excellence in professional associations. The SfE BES conference is our Society's flagship event, designed to bring together the best in UK and international endocrinology. We are thrilled that it has been recognised in this way.



Recognising excellence in Professional & Trade Associations



SOCIETY CALENDAR

26 February 2015
NATIONAL CLINICAL CASES MEETING
London

16–17 March 2015
ENDOCRINE NURSE UPDATE
Birmingham

16–18 March 2015
CLINICAL UPDATE
Birmingham

12–15 April 2015
BNA 2015: FESTIVAL OF NEUROSCIENCE
Edinburgh

2–4 November 2015
SOCIETY FOR ENDOCRINOLOGY BES CONFERENCE 2015
Edinburgh

see www.endocrinology.org/meetings for full details



GRANT AND PRIZE DEADLINES

11 March 2015
SUMMER STUDENTSHIPS

15 March 2015
CONFERENCE GRANTS

10 April 2015
EARLY CAREER PRIZE LECTURE ABSTRACTS

4 MAY–6 JULY 2015
SfE BES REGISTRATION GRANTS

27 MAY 2015
EARLY CAREER GRANTS

27 MAY 2015
EQUIPMENT GRANTS

15 JUNE–13 JULY 2015
UNDERGRADUATE ACHIEVEMENT AWARDS

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

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

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



JOURNAL OF ENDOCRINOLOGY

Progesterone-induced decorin suppresses endometriosis

Endometriosis affects 1.5 million UK women. Endometrial cells migrate outside the uterine cavity, often to the ovaries. Symptoms include pelvic pain, dysmenorrhea, dyspareunia and infertility. Gonadotrophin-releasing hormone (GnRH) agonists and progestins are used as treatment, but not without side effects.

Ono and colleagues have investigated the effect of dienogest, a progestin without systemic androgen activity, on endometrial cells *in vitro*. Both dienogest and progesterone elicited anti-proliferative effects on endometrial epithelial and stromal cells through the upregulation of decorin expression.

Decorin, a small proteoglycan in the extracellular matrix, was also increased in patients treated with dienogest.

This provides useful insights into progestin action on endometrial cells. Progestins, which are oestrogen-independent, may provide treatment regimens that are preferable to GnRH agonists, which cause hypo-oestrogenic side effects, such as hot flushes and bone loss. Whether decorin can be targeted as a treatment for endometriosis and other conditions where it has been shown to act as a tumour repressor requires further study.

Read the full article in *Journal of Endocrinology* **233** 203–216 (OA)

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Acetylation regulates PPAR γ and adipogenesis

Peroxisome proliferation-activated receptor gamma (PPAR γ) is a transcription factor with important roles in adipogenesis, glucose and lipid metabolism. Thiazolidinediones (TZDs), through their action on PPAR γ , are used to treat type 2 diabetes, but have significant side effects. Alternative methods to control PPAR γ activity may provide preferential treatments.

Jiang and coworkers have characterised the activity of acetylated PPAR γ resulting from the inhibition of histone deacetylase 3 (HDAC3). They suggest a model whereby PPAR γ is acetylated in the absence of ligand, and is modulated by presence of the corepressor, which includes HDAC3.

Dissociation of HDAC3 from PPAR γ enables acetylation levels to increase, activating PPAR γ and inducing expression of PPAR γ target genes, potentially by recruitment of histone acetyltransferases.

This indicates that inhibition of HDAC3 may be an alternative way of controlling PPAR γ activity and so treating type 2 diabetes without the side effects associated with TZDs. Further studies are required to establish whether HDAC3 inhibition affects adipogenesis and insulin sensitisation *in vivo*.

Read the full article in *Journal of Molecular Endocrinology* **53** 191–200

ENDOCRINE-RELATED CANCER

Castration promotes cancer cell growth in bone

Prostate cancer is one of the most common cancers among UK men. Most cases arise as androgen-dependent tumours that regress under androgen ablation therapy. The disease often becomes androgen-independent, at which point there is no effective treatment and metastatic spread results in lethality.

Metastasis to bone is common, where the microenvironment and increased bone turnover contribute to tumour growth and progression. Ottewill and colleagues have used *in vivo* models to show that androgen ablation caused reduced bone volume and increased the incidence and growth

of disseminated prostate cancer cells in bone. This was reversed by administration of zoledronic acid (ZOL), which inhibits osteoclast activity and bone turnover.

ZOL is currently licensed to treat bone complications arising from androgen deprivation. Earlier administration of ZOL, in conjunction with androgen deprivation, may be beneficial in reducing bone loss and preventing prostate cancers metastasising to bone. A phase III clinical trial is underway to determine whether early ZOL administration is beneficial in prostate cancer.

Read the full article in *Endocrine-Related Cancer* **21** 769–781



ENDOCRINE HIGHLIGHTS

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

Generation of human pancreatic β cells *in vitro*

Type 1 diabetes (T1D) results from the autoimmune destruction of pancreatic β cells causing loss of insulin secretion and glucose homeostasis. Transplantation of pancreatic islets enables better glucose homeostasis than is achieved with exogenous insulin administration. The utility of transplantation is limited by a lack of donor islets, so other sources of functional human β cells are required.

Rezania *et al.* and Pagliuca *et al.* have described the differentiation of human stem cells into functional insulin-secreting β cells *in vitro*. Both protocols give rise to appreciable numbers of insulin-positive cells, indicating that large scale β cell production could be achieved. The β cells were also shown to function *in vivo* in mouse models of T1D to improve glucose homeostasis.

This provides promise for the use of transplanted β cells in T1D, as well as provision of material for pharmacological studies. The degree to which these cells resemble normal endogenous human β cells is unclear and this requires further investigation.

Read the full articles in *Nature Biotechnology* **32** 1121–1133 and *Cell* **159** 428–439

CLINICAL ENDOCRINOLOGY

Opposing effects of calorie restriction and gastric bypass on FGF21 in obesity

Lips *et al.* set out to investigate the effect of different weight loss strategies on levels of fibroblast growth factor 21 (FGF21) in morbidly obese subjects with normal glucose tolerance (NGT) versus those with type 2 diabetes (T2D). FGF21 has diverse metabolic functions in both the fed and food-deprived states, with expression regulated by fasting and feeding.

Patients with NGT were treated with either gastric banding or Roux-en-Y gastric bypass (RYGB) to achieve weight loss, while patients with T2D

achieved weight loss through RYGB or a very low calorie diet. Patients' levels of FGF21, FGF19 and bile salts were measured before intervention, and 3 and 12 weeks post-intervention.

Calorie restriction by gastric banding or a very low calorie diet lowered FGF21 and bile salts, while RYGB raised these levels. As FGF21 is known to have beneficial metabolic effects, the raised levels of the substance after RYGB may contribute to this treatment's success in improving glucose homeostasis.

Read the full article in *Clinical Endocrinology* **81** 862–870

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Glucagonoma-induced acute heart failure

Zhang *et al.* report a 51-year-old woman with glucagonoma who presented with left ventricular heart failure and developed cardiogenic shock despite treatment. Glucagonomas (glucagon-producing pancreatic tumours) are a fairly rare type of neuroendocrine tumour (NET) and are usually associated with conditions such as multiple endocrine neoplasia type 1 (as was the case here).

The patient was treated with an i.v. infusion of the somatostatin analogue octreotide and cardiac function steadily improved. Measures of

chromogranin A as a tumour marker were found to be significantly elevated, and these decreased as the patient showed clinical improvement.

NETs (other than carcinoid tumours) have not previously been linked with heart failure. The authors suggest that the glucagonoma was the causal factor for heart failure in this case, and that cardiac function should be monitored routinely in all NET patients.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* 2014 EDM140061 (OA)

ENDOCRINE CONNECTIONS

Stress in patients with diabetes and heart disease

The incidence of depression and stress is elevated in patients with diabetes and also in those with heart disease, with stress being an established risk factor for poor outcome in both groups.

The psychological burden of suffering from diabetes and ischaemic heart disease simultaneously was assessed by Bergmann and colleagues using a variety of questionnaires and the pressure pain sensitivity test. They found that patients with both diabetes and heart disease had increased depressive

symptoms. The incidence of chronic stress was elevated compared with the general population, but was similar between patients with heart disease and those with both conditions.

Overall the study indicates that clinicians should account for psychological symptoms, especially depression, when treating patients with multiple chronic disorders.

Read the full article in *Endocrine Connections* **3** 156–160 (OA)



Jet-lag, obesity and disruption of the gut microbiome

Thaiss and coworkers have demonstrated that the circadian rhythms of the gut microbiome in mice and humans are disturbed by changes in the host's biological clock, resulting in obesity and the metabolic syndrome.

Humans have only relatively recently significantly altered their circadian rhythms, due to lifestyle changes such as shift work or flights across time zones. This behaviour has been linked to diseases including diabetes, obesity and cancer, but a link to the circadian clock had not previously been investigated.

The microbial content of faecal samples from mice and humans was found to change in line with rhythmic fluctuations associated with the host's biological clock. When mice endured changing light-darkness schedules and abnormal feeding habits, the gut microbiome lost its rhythm and altered in composition. When combined with a high fat diet, these jet-lagged mice gained weight and developed various metabolic symptoms associated with diabetes. Furthermore, in jet-lagged humans, the composition of the gut microbes also altered, favouring the proliferation of bacteria linked to obesity and metabolic disease.

Read the full article in *Cell* **159** 514–529 (OA)

Novel intraoperative imaging modality for parathyroid identification

Accurate identification of parathyroid glands during thyroidectomy or parathyroidectomy is vital to the procedure's success. Their variable location, generally small size and inconspicuous colouring all make this difficult.

McWade *et al.* report recent progress with their use of near-infrared (NIR) autofluorescence imaging to identify the parathyroid gland intraoperatively. Certain molecules demonstrate autofluorescence when stimulated by light in the NIR spectrum, and the authors postulate the presence of such a fluorophore in parathyroid tissue.

Measurements of NIR autofluorescence in various tissues in 110 patients undergoing neck surgery

demonstrated up to 25 times more signal from parathyroid tissue than thyroid, with no signal from muscle or fat. Next, they customised a clinical endoscope camera with an NIR laser and appropriate filters to collect real time, *in vivo* NIR fluorescence images in six patients, successfully identifying parathyroid tissue each time.

The identity of the fluorophore is unconfirmed, but the calcium-sensing receptor is the prime candidate.

Read the full article in *Journal of Clinical Endocrinology & Metabolism* **99** 4574–4580

Leptin links obesity and blood pressure

Obesity has long been recognised as a risk factor for the development of hypertension. Although several strong lines of evidence have previously implicated the neuronal circuitry involved in energy homeostasis in this phenomenon, the precise mechanism linking an increase in fat mass with an increase in blood pressure has remained elusive.

In a tour de force of murine metabolic phenotyping, Simonds *et al.* have demonstrated that the adipokine leptin, acting on a small population of neurones within the dorsomedial hypothalamus, is the link between weight gain and changes in blood pressure. They neatly combined these data with findings from leptin-deficient subject who had received leptin replacement therapy, as well as measurements from obese patients who had lost significant amounts of weight through adherence to a rigorous diet and exercise regimen.

These findings highlight a potential novel therapeutic avenue for the treatment of obesity-associated cardiovascular disease.

Read the full article in *Cell* **159** 1404–1416

THE FANTASTICAL WORLD OF HORMONES

WRITTEN BY JOHN WASS



The history of the discovery of hormones abounds with bizarre experiments, remarkable characters, wrong turns, opportunism and quackery. However, there are elements of genius and amazing tales of survival. The endocrine system may have been the last to really be discovered, because it is not an anatomical one.

THE VOICE OF AN ANGEL...

It is difficult to know where to start, but perhaps interesting in concept is the 'castrato', a famous presence in opera in the 16th, 17th and 18th centuries. Castrati were, of course, operated on before puberty, and hundreds of thousands of them (often from poor families) went through the operation until the early 20th century. There is an amazing recording from 1902 of Moreschi, the last papal castrato. Perhaps the most famous castrato is Farinelli, whose picture can be found in Handel's house in London, and who sung for the 'mad' King of Spain every night. He had a star career, and perhaps it was this aspiration that led many poor parents to put their sons through such an awful operation.

The voice of a castrato was pure and forceful, and they had amazing breath control. This was largely because their ribs carried on growing and so they had an enormous lung capacity. Of course they experienced other changes; there was no temporal recession, and their arms and legs were long. The practice continued until the 20th century, by which point people perhaps realised what was going on.

ELIXIR OF LIFE?

Interestingly, it was in 1849 that some experiments by Berthold, a German physiologist in Göttingen, began to explain the endocrinology involved (although Berthold did not realise this). He experimented on capons, a great delicacy at that time because of their tender meat. These birds were very docile, and the reason for this was their testes had been removed. It was easy to see which these birds were, because the cone (the red bit on the head of the cockerel) was droopy, as was the waffle (the red bit below the jaw). Berthold transplanted testes from intact birds into the capons' abdomens, and showed that they redeveloped normal male characteristics. When he did a post mortem, he found that the testes had redeveloped their blood supply. However, his discoveries made no impact, and ultimately this was a missed opportunity.

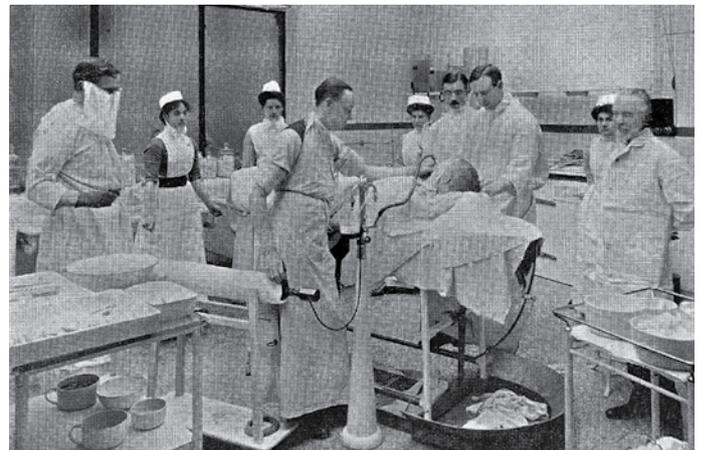
The next amazing story is that of the famous neurologist Brown-Séquard who, in 1889 at the age of 72, reported to the Academy of Sciences in Paris that he had injected himself with a mixture made up of the blood from testicular veins, semen, and juices of the testicles of dogs or guinea pigs. He reported a marked improvement in his strength, stamina and ability to concentrate. As might be predicted, his experiments were not reproduced, although they caused considerable excitement throughout Europe.

PINK THYROID JUICE

One of the next exciting discoveries was made by Victor Horsley, a famous surgeon, who had a famously huge social conscience and was a forcible advocate of free health care for all. He showed that, by removing the thyroid from monkeys, they developed the changes of myxoedema, just like humans. Their hair fell out and they became

lethargic. This demonstrated that myxoedema was caused by thyroid deficiency and he suggested transplanting tissue from sheep's thyroids into human patients.

Obviously this was not a long term cure. However, a pupil of Horsley's, George Murray (a physician in Newcastle upon Tyne), cut sheep's thyroids into small parts and put them into carbolic acid, stoppered them overnight and then filtered them through a handkerchief. This product he called pink thyroid juice, and he injected it into a 46-year-old female patient. Within 3 months, there was a miraculous improvement in her appearance and her skin was less pale and her energy improved. He carried on with regular injections and this patient lived to the ripe old age of 74.



Sir Victor Horsley in the operating theatre in 1906, National Hospital, Queen Square, London ©Wellcome Library, London

This great fashion for injecting extracts of glands into people worked for the thyroid, but not in Brown-Séquard's scenario, obviously because of the very different half lives of the two hormones.

OVARIAN HYSTERIA

Up until the late 1800s, the ovary was thought to be part of the nervous system. Viennese gynaecologist Chobrak started removing the ovaries of women in order to treat such conditions as hysteria, anorexia, anxiety and even nymphomania. Joseph Howden in Vienna took the ovaries and transplanted them into guinea pigs. He showed that these reversed the changes caused by oophorectomy. Obviously they had lost their nervous connections, and this discovery effectively put an end to the use of oophorectomies. It had a huge implication for the story of hormones as well.

'He had injected himself with ... juices of the testicles of dogs or guinea pigs. He reported a marked improvement in his strength, stamina and ability to concentrate.'

ENTER 'THE HORMONE'

Ernest Starling was the first to coin the term 'hormone', in the very early years of the 20th century. The story goes that Starling was talking to a colleague at a Cambridge dinner, and they were both struggling for a name for these secretions that could pass through another part of the body and stimulate it directly. A scholar of ancient Greek suggested the word '*ormao*', the Greek word for 'excite' or 'stir up' – and thus the word 'hormone' entered the language.

'Numerous Steinach operations were performed ... Even WB Yeats had an operation ... and reported that it improved his creative powers.'

Obviously many hormones have since been identified, such as growth hormone in 1932. The discovery of insulin slightly predates that of growth hormone. It had been known since the 19th century that if the pancreas was removed from dogs they developed diabetes. The problem encountered in studying the pancreas, of course, was that it makes exocrine and endocrine compounds, and the difficulty was really separating these.

Frederick Banting, the unlikely discoverer of insulin, was a failed GP in Canada who used to supplement his income by giving lectures to medical students. It is said that, in the middle of the night, he hit upon the idea of ligating the pancreatic duct while keeping the dogs alive. Using this approach, the exocrine part of the pancreas became inactive. After 6 weeks, the dogs were sacrificed and their pancreases removed, which enabled insulin to be extracted.

The first injection of insulin into Leonard Thompson occurred in 1921, when he was 14 and only days away from death. He was incredibly thin and smelled of acetone. The 'muck' made from a dog's pancreas gave Thompson a whole new lease of life – and the rest, of course, is history.

Frederick Banting ©Wellcome Library, London



'Glanoid', an early example of a hormone supplement used to treat anaemia, amenorrhoea and menorrhagia.

©Science Museum, London, Wellcome Images

TIED UP IN KNOTS

Before we get to the modern day, there was one last amazing wrong turn! Eugen Steinach was a Viennese scientist working in the Biological Research Institute in Vienna. His theory was that if you tied off the duct from the testis (i.e. a modern vasectomy) you would increase the amount of testosterone it produced. Numerous Steinach operations were performed around the world, with the aim of increasing the amount of testosterone. Even WB Yeats had an operation, at the age of 69, and reported that it improved his creative powers. Some say he produced his best poetry after the procedure. He also took up with a 27-year-old actress (42 years his junior)!

LAST WORD

Endocrinology never stands still, and this very selective run through some aspects of its history omits many recent triumphs, due to lack of space. The account would not be complete, however, without mentioning the discovery of leptin and the amazing work of Steve O'Rahilly and Sadaf Farooqi in Cambridge, in examining genetic causes of obesity with such huge success.

Indeed, as you continue your studies, never forget that you are adding to the rich and fantastic trail left by all those endocrinologists who have preceded us!

JOHN WASS

Professor of Endocrinology, University of Oxford
Academic Vice-President of the Royal College of Physicians, London

To find out more about 'The Fantastical World of Hormones', watch John Wass' documentary on the subject, which also features Sadaf Farooqi and Saffron Whitehead, and was first aired on BBC4 in February 2014. You can view the full documentary at <http://bit.ly/1IToJeK>.



PITUITARY SURGERY: A HISTORICAL PERSPECTIVE



WRITTEN BY GRAHAM R DOW

The history of pituitary surgery is a fascinating insight into the work of surgical pioneers. Nearly abandoned at one stage, the transsphenoidal operation was improved stepwise by developments such as radiographic screening and the operating microscope, and propagated by sharing practice between Europe and North America. As Michael Powell relates in his personal account (page 10), this continues today with developments in endoscopic pituitary surgery. It is worth looking back, and considering our surgical ancestors who have left their mark, and the knowledge on which their endeavours were based.

ACROSS THE MILLENNIA

Although documentation of yet-to-be-characterised pituitary disorders may date to ancient Egypt (a pharaoh depicted in 1365 BCE shows features of acromegaly), it was Galen who, in 150 CE, first described the pituitary gland. It was suggested that it drained phlegm from the brain to the nasopharynx.

In the 18th century, various pituitary disorders were described, including amenorrhoea, acromegaly and diabetes insipidus. However, it wasn't until 1887 that Minkowski first linked expansion of the pituitary gland to several clinical syndromes. This led to acceptance that anatomical expansion was what produced these syndromes, and the natural interest in operating on the pituitary.

THE INITIAL APPROACH

The first documented transnasal operation to successfully remove a pituitary tumour was performed by Austrian neurosurgeon Hermann Schloffer in 1907, using a superior nasal approach. In 1909, Harvey

Cushing at the Johns Hopkins Hospital in Baltimore performed his first pituitary operation on a patient with acromegaly, using Schloffer's original technique. He went on to use a sublabial transsphenoidal approach in more than 200 patients between 1910 and 1925.

Cushing was initially a clear proponent, encouraging many others along the way. However, once he had done 272 transsphenoidal operations, his views altered. He perceived disadvantages of poor access to extensive suprasellar masses and difficulties in dealing with some types of tumour. He felt that the extent of resection was usually suboptimal and, quite abruptly, he changed to a transcranial practice and abandoned transsphenoidal surgery.

Most surgeons at the time were so influenced by his practice that they followed suit and, for a while, the transsphenoidal operation was regarded with a degree of contempt. Indeed, if it hadn't been for a certain young Scotsman, the transsphenoidal approach may have remained in the wilderness.

TRANSPHENOIDAL REVIVAL

The young Scotsman was Norman Dott who, at the age of 26, was already a Fellow of the Royal College of Surgeons of Edinburgh and setting up practice. He undertook a fellowship with Harvey Cushing in 1923. Cushing taught him the transsphenoidal approach, and Dott analysed what he learnt. Perhaps his engineering background (Dott was an engineering apprentice before attending medical school) was a factor in the difference between his conclusions regarding the approach and those of his mentor Cushing.

As Cushing began to favour transcranial surgery, Dott concluded that there was a great intrinsic advantage in surgery from below in permitting the growth to enlarge downwards away from the chiasm, especially as most lesions would not be removed entirely anyway. On his return to Edinburgh, he introduced the transsphenoidal approach to his neurosurgical practice, and designed a lit nasal speculum retractor. Throughout much of Dott's career, most of the neurosurgical community still shunned the transsphenoidal procedure as Cushing latterly had, but Dott achieved great results with it, enough to impress visiting Parisian surgeon Gerard Guiot.

FLUOROSCOPY AND MICROSCOPY

Guiot observed Dott during a 2-week placement at the Royal Infirmary of Edinburgh in 1956, and began to use transsphenoidal surgery in Paris, introducing fluoroscopy and cisternal pneumography to guide instruments to the skull base and visualise the suprasellar contour. Guiot questioned the general reluctance to use transsphenoidal surgery and, in a career in which he operated on more than 1,000 cases, demonstrated superior results to transcranial surgery with lower morbidity and better visual recovery.

Fragmentary limestone face of Akhenaten, the Egyptian pharaoh who is thought to show features of acromegaly

© The Trustees of The British Museum





Harvey Cushing,
in theatre gown and gloves
©Wellcome Library, London

The baton then passed to the Canadian neurosurgeon Jules Hardy, who spent time with Guiot in 1961–1962, before returning to Montréal. Hardy introduced the surgical microscope to better illuminate and visualise the narrow surgical field. With this he began to appreciate differences between adenomatous tissue and normal gland. By selectively removing tumour and leaving normal gland, he restored pituitary function in many patients.

He also became convinced of the presence of microadenoma in hypersecreting disorders, as opposed to what was believed to be diffuse hyperplasia. Hardy described microadenoma as ‘the pimento in an olive’, but was met with much scepticism in 1968 when he presented the concept. It

was finally accepted a decade later, and selective microadenectomy was the standard treatment in Cushing’s disease and acromegaly.

Hardy developed microinstruments for use in pituitary surgery specifically mounted on bayonet handles to be used at depth without obscuring the surgeon’s view. The successor to Cushing, Dott and Guiot, many would probably credit Hardy for his contributions in advancing microscope pituitary surgery to the modern era.

THE AGE OF ENDOSCOPY

Endoscopic pituitary surgery excites a lot of interest nowadays. Guiot was probably the first to use the endoscope for transsphenoidal surgery, in 1961. At the time he did not feel it gave good enough visualisation and only occasionally used it after removal of a tumour to inspect the floor of the sella.

After Karl Storz licensed the idea of fibre optic external light transmission coupled with a rod lens optical system in 1965, many advances were made, particularly in otorhinolaryngology, where those such as Draf, Stammberger and Kennedy popularised endoscopic sinus surgery. In the 1970s, Apuzzo and others reported endoscopy as a technical adjunct during microscopic pituitary surgery. Subsequently, Perneczky introduced the concept of minimally invasive neurosurgery, emphasising that the endoscope allowed panoramic appreciation of the anatomy not apparent with the microscope.

Jho and Carrau (a neurosurgeon and an otorhinolaryngologist) from Pittsburgh are recognised for pioneering pure endoscopic endonasal surgery for pituitary tumours in the late 1990s. Cappabianca in Naples reported his early experience and, with others, contributed hugely to the development of techniques and instrumentation. An explosion of interest in endoscopic skull base surgery has followed, expanding indications from pituitary lesions to many additional pathologies. There continues to be much sharing of results and comparison of endoscopic and traditional techniques.

‘Hardy described microadenoma as “the pimento in an olive”, but was met with much scepticism in 1968 when he presented the concept.’

Many other modern ideas stand to serve pituitary surgery well, such as image-guided surgery, intra-operative magnetic resonance imaging, and advances in functional imaging of secreting pituitary tumours. However, many of the operating techniques, particularly at the level of the sella, still have their basis in the contributions of the early pioneers – Cushing, Dott, Guiot and Hardy – who shall not be forgotten.

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PITUITARY SURGERY IN THE UK: A PERSONAL JOURNEY

WRITTEN BY MICHAEL POWELL

In 1975 when I qualified, most neurosurgical pituitary procedures were carried out for loss of vision from chiasmatic compression using a craniotomy, a situation that was to last for more than a decade. There was some endocrine pituitary surgery, but it was performed at only a few centres, mainly by ear, nose and throat (ENT) surgeons, using a variety of transsphenoidal approaches. The third indication was for control of metastatic breast and prostate tumours.

I wanted a surgical career, but had chosen orthopaedics, as most medical students had decidedly limited exposure to neurosurgeons. At that time there were very few – probably only about 100 – who were thinly spread across more centres than today, and often in odd places, such as Pinderfields (Leeds), Atkinson Morleys (south west London) and Smethwick (Birmingham): well away from the ivory towers of medical school hospitals.

In Bristol, the Professor of Medicine (a gastroenterologist) decreed that clinical neuroscience was ‘a postgraduate study’. A few medical schools, such as that in Newcastle upon Tyne, had strong units embedded, and thus produced a substantial cadre of neurosurgeons. ‘Get them young,’ as they say.

Of the 12 London medical schools, only 2 had full-time neurosurgical units, and some none at all. At the Middlesex, although we had a strong neuroscience tradition, the single part-time neurosurgeon was a decidedly difficult character, and we students were kept well away from him.

The majority of neurosurgeons would do anything. Some worked single-handed and, particularly in the two-man units, the neurosurgeons communicated through their juniors or their secretaries, as the stresses made for some extremely dysfunctional people. Superspecialism was extremely rare.

GETTING A TRAINING

Specialty training in the 1970s and 1980s was very random. We drifted around the country competing for jobs at senior house officer, registrar and senior registrar level. There was no seamless training, and no monitoring of what was supposed to be training. I moved from London through Norwich, Oxford and Bristol before ending up back in London. And I was lucky!

For surgeons, the demands of a ‘general’ FRCS were 18 months of ‘general’ surgery, 6 months of ‘casualty’ and two 6-month periods in any of the smaller surgical specialties. Neurosurgery was sometimes included as a much-disliked option. Once in a senior registrar post, one stayed there until one was appointed consultant (dead man’s shoes) or was dismissed (it happened). This could go on for more than a decade, as there was no fixed senior registrar period. Luckily, I occupied this role for just 23 months.

I was also lucky as I got a Bristol senior house officer rotation that included neurosurgery working under some of the most charismatic

men of the era, particularly Huw Griffith. When I expressed an interest in a neurosurgical career, I was invited to take the next registrar job, which conveniently arose as soon as I got my FRCS. Just like Napoleon’s generals, it was good to be lucky.

There was also no 48-hour week European Working Time Directive to consider either. All my registrar and senior registrar time was in 1:2 rotas, meaning starting alternate Fridays and staying on call until Monday evening – 80 hours on the trot. We got a lot of first-hand experience. I have to say I loved it and never felt over-stressed, although I certainly felt tired on occasions.

‘I remember one old man with a recurrent macroadenoma asking me if he would be unconscious again for 2 weeks following his operation.’

ARRIVAL OF NEW TECHNOLOGIES

It was an exciting time for neurosurgery, as CT scanning (on an ‘EMI scanner’) was just entering general use. Bristol had the fourth machine in the country, and diagnosis had moved from a black art to an accurate science.

The other change was the use of the operating microscope. Neurosurgeons in the UK were slow adopters of the microscope but, by the time I entered training, the younger and more forward British neurosurgeons were using it for a range of procedures. Nevertheless, this was still the era in which the old guard scorned the microscope even for aneurysm clipping.

PITUITARY SPECIALISM

So, what about pituitary tumours? The luckless patient would usually have theirs removed at a craniotomy by someone doing only a couple per year, possibly even by a registrar like me with no specialist training at all. This seemed very dangerous. Many patients were confused and sleepy for a good few days afterwards. I remember one old man with a recurrent macroadenoma asking me if he would be unconscious again for 2 weeks following his operation, anticipating his own death (you’ll be pleased to hear he did well). I saw a lot of cranial pituitary surgery as a senior registrar in London in 1983, but it was only when I trained under a master technical surgeon (and role model), Lindsay Symon, that I saw how safe it could be.

I had been fortunate to have a substantial grounding in the pituitary, having spent my ‘gap year’ cutting sections of vole pituitary and hypothalamus in Geoffrey Harris’ laboratory in Oxford, and even considered a DPhil in reproductive endocrinology. At the Middlesex, I had spent a long time on the firm of Sir John Nabarro, whose lab contained most of the future professors of endocrinology in London by the time I was appointed a consultant. On Nabs’ unit, acromegalics got transsphenoidal surgery by an ENT surgeon, whilst patients with Cushing’s had a bilateral adrenalectomy via a huge abdominal incision performed by the Professor of Surgery (and then a long time in the intensive therapy unit), followed by radiotherapy.

ADOPTING THE TRANSSPENOIDAL APPROACH

As a registrar, Huw Griffith introduced me to transsphenoidal surgery. A Bristol ENT surgeon, Jack Angell-James, had been undertaking some using an ethmoidal approach through an incision at the bridge of the nose. Huw thought he could improve on this, and designed some special 'kit'. Having got the practice, he also realised that pituitary patients spent a great deal of time between endocrine, neurosurgical and oncology clinics, and so invented the multidisciplinary pituitary clinic with an endocrinologist from Bath.

Transsphenoidal surgery had been around for a long time, having been demonstrated in 1907 in Austria, before being 'transplanted' to Boston by Cushing, subsequently then being abandoned there but continued in Edinburgh, whence it was taken to be developed in Paris, where fluoroscopy was introduced, prior to moving to Montréal, where Jules Hardy introduced the microscope in 1972.

Most transsphenoidalists used Cushing's sublabial approach, standing in the patient's axilla, across the chest, with the initial incision being by direct vision. Many used a two-man team, the ENT surgeon making the approach and the neurosurgeon taking out the tumour.

In Bristol, impatient Huw adopted a direct nasal approach performed entirely alone, using specially designed instruments, going through the nostril, pushing the turbinates aside and breaking through the base of the septum at the sphenoid ostia directly into the sphenoid. He did it all with the microscope. Microscopes were rather primitive, so the assistant saw little. However, by the time I arrived as a senior registrar in London, I had already undertaken about 15 cases personally in my 2 years at registrar level.

TIME FOR REFINEMENT

Arriving in London as a senior registrar in 1983, I discovered that things had changed since I had left as a 1976 pre-registration houseman. A few neurosurgeons in London – probably about seven of the younger ones – were now doing transsphenoidals, and what a palaver! It was all done by the Cushing method and took ages (regularly about 4 hours). In Bristol it seldom took an hour; we were encouraged to be speedy as there was a lot of work.

The London results seemed no better for, once at the pituitary, it was a hasty scoop around and out – no fine dissection. In fact, the 4-hour boss taught that surgery was simply a biopsy and the cure was the radiotherapy. Everyone got radiotherapy regardless, following a methodology established by Barts, spending a minimal amount of time on the neurosurgical unit and being whisked back to the medical wards as soon as they had recovered from the anaesthetic. Consequently, few surgeons had the faintest idea about endocrine levels or, indeed, audited their results.

Becoming a consultant in 1985, I found myself back at my old medical school, where ENT surgeons were still doing the pituitaries. However, Middlesex had combined with University College Hospital (UCH), where the Professor of Endocrinology was a mate of my senior neurosurgical partner, and they held a shared pituitary clinic together. I was allowed to join them, having been discovered by the Middlesex Professor of Endocrinology, the wonderful Howard Jacobs, who adopted me when the ENT surgeon lost his bottle after a surgical disaster, and declared all tumours only suitable for craniotomies.

When I informed Howard that I could 'do' transsphenoidals, he was delighted. I think he enjoyed finding a surgeon who knew a bit about hormone levels. It helped that he had taught me as Nabs' senior registrar. Shortly after that, he was telling other endocrinologists about this new marvel, and the equally charismatic paediatric endocrinologist Charles Brook adopted me for the kids as well.

'A few neurosurgeons in London were doing transsphenoidals, and what a palaver! It took ages. In Bristol it seldom took an hour; we were encouraged to be speedy as there was a lot of work.'

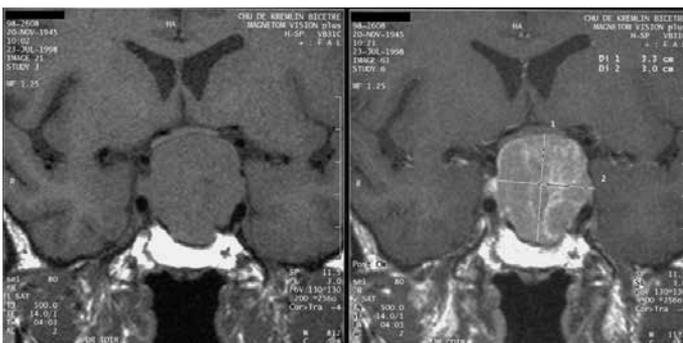
Grasping the opportunity, back at the National Hospital where I held some of my consultant sessions, I joined the monthly pituitary clinic run by a trio of powerful Queen Square and Moorfields neurologists, led by Ian McDonald. He held the clinic without a neurosurgeon and from here dished out the macroadenomas by rote to the four neurosurgeons. The first to be referred to me was not an adenoma at all but a giant aneurysm. Luckily, I realised this and involved one of my mentors – after asking Ian's permission, much impressing him. Soon, I was doing them all.

LEARNING FROM THE MASTERS

I also was able to study a few of the masters of pituitary surgery. Rudolph Fahlbusch visited my then boss, Lindsay Symon, and invited me to visit him in Erlangen. There, I assisted him in seven operations in 2 days: astonishing and wonderful, generous training. In a similar way, I had met Ed Laws, then in Washington, DC, at the first meeting of the International Society of Pituitary Surgeons, and had been invited with great generosity to his home. I was fortunate to observe Ed Oldfield of NIH do three Cushing's procedures in a revelatory afternoon, and met and spent time with another, rather forgotten, great, Alex Landolt of Zurich.

Pituitary macroadenoma with suprasellar extension, compressing the optic chiasm

© Philippe Chanson and Sylvie Salenave



CONTINUED ON PAGE 12...

I had seen them all doing painstaking dissection within the fossa – the dissection of the tumour taking more time than the approach, unlike in my training. Each, particularly Rudo, stressed the importance of understanding the endocrinology and talking to endocrinologists, not neurosurgeons. Finally, they encouraged me to keep my own database, to monitor my outcomes – visual, endocrine and complications. It's an expensive hobby, but I have never regretted having set one up.

DEVELOPMENT OF THE SUPERSPECIALISM

By the start of the 1990s, I was doing the majority of the pituitary surgery at the National and all the NHS practice at UCH/Middlesex, so undertaking well over 50 cases per year, a big number for the time. I was not the only one, as two rather more senior surgeons, Adams in Oxford and Teasdale in Glasgow, had developed substantial practices, draining cases away from regions where the neurosurgeons were unable to subspecialise. Endocrinologists had woken up to the fact that superspecialists were better. Even better were the interdisciplinary meetings such as the European workshops.

'I had seen them all doing painstaking dissection within the fossa – the dissection of the tumour taking more time than the approach, unlike in my training. Each stressed the importance of talking to endocrinologists.'

Pituitary disease had also benefited from significant advances in diagnostic technology. Magnetic resonance imaging, introduced in the mid-1980s, had become the new imaging modality and we could at last 'see' the microadenomas, rather than infer their presence. Endocrine testing improved. No longer did it take a week before the prolactin result came back, or a whole month for growth hormone data.

Patients with acromegaly and Cushing's were following set investigatory protocols, although the Barts and non-Barts schools (the latter including us!) endlessly bickered about which was the correct way. Some neurosurgeons had realised that prolactinomas were better treated with bromocriptine, although I fondly remember the great Jules Hardy likening 'Parlodol' to patent creams for piles.

IMPLEMENTATION OF GUIDELINES

By the mid-1990s, the movers and shakers of endocrinology had decided enough was enough in amateur pituitary disease management. A group from the Royal College of Physicians of London, led by John Wass, decided to set out some guidelines for management.¹ I was one of the neurosurgeon advisors.

The guidelines were both modest and sensible, hinting at the need for subspecialisation and suggesting that overall care of the patient should be led by an endocrinologist. They were published widely but,

depressingly, in *British Journal of Neurosurgery*, the editorial comment was that there was 'much for a neurosurgeon to disagree with'.

This was the time of the Manchester series, published on the outcome of surgery for acromegaly in their region.² Here, three neurosurgical units could not nominate a single specialist surgeon for pituitaries, so none operated on more than seven cases per year, with the inevitable consequence of a <17% remission rate. Concurrently, an endocrine group from New York published an admirable 68% remission rate using a single specialist surgeon.³ Happily, with the fusion of the three units and the adoption of a specialist pituitary surgeon, Manchester's results are now excellent.

THE DAWN OF ENDOSCOPY

With a move towards specialist pituitary surgeons, there came a new challenge from outside the field. Whilst visiting Ed Laws in 1996, I was asked to look at a paper that had been submitted to a journal he was editing. A Philadelphia neurosurgeon claimed he was doing surgery with an endoscope. Although seemingly most unlikely, Dr Laws had sent 'a spy', and it appeared to be true.

Endoscopy had been around for a while. It had never found a place in neurosurgery, although Huw Griffith had tried it for intraventricular tumours. But, by the millennium, endoscopy was catching on, albeit in small numbers. Now, 15 years later, it is largely replacing those dinosaurs, such as myself, who never quite got the technique (despite having bought the equipment in 1998 and tried for a few years). Certainly, all my best former trainees use it in preference to the microscope, although no one has ever shown a true advantage, at least not in endocrine or visual outcomes.

MODERN TRAINING AND COLLABORATION

With the introduction of endoscopy came another great improvement. Workshop training and specialist fellowships have made a huge difference to young neurosurgeons' skills when starting their consultant posts. I am pleased that our hospital introduced the first of both of these in the UK, although they are now commonplace everywhere.

Finally the adoption of multidisciplinary team meetings, despite their cumbersome nature, has much improved the overall care of the pituitary patient, and there is no longer a single unit in the UK that does not have both a specialist surgeon and a regular team meeting.

Added to this, pituitary specialist nurses sort out continuity of care issues and an active patient self-help charity (The Pituitary Foundation) is a wonderful asset. On the whole, the patient nowadays has a good chance of excellent care that is nearly standardised across the UK.

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THE STORY OF PARATHYROID SURGERY

WRITTEN BY F FAUSTO PALAZZO



The parathyroid glands were the last organs visible to the naked eye to be described. In 1850, Sir Richard Owen, curator of the Natural History Museum, described 'a small, compact, yellow glandular body attached to the thyroid' during the dissection of an Indian rhinoceros that died in London Zoo (see right).



Left tonsil and half the larynx of a male rhinoceros, showing the thyroid and parathyroid glands in position, prepared by Richard Owen, 1850

©Courtesy of the Hunterian Museum at the Royal College of Surgeons, RCSHM/L 333.1

In 1887, Ivar Sandström, a 25-year-old medical student at the University of Uppsala, confirmed the existence of the newly discovered organ in 50 human cadavers. Even at that stage, he described the great variation in position, vascular supply and appearance of the glands that represent part of the 'mystique' of parathyroid surgery to this day. By virtue of the position of the glands, Sandström first suggested using the name 'glandulae parathyreoidae', but his manuscript was rejected by the leading German journals of the time, which contributed to him not receiving the acclaim he deserved during a lifetime sadly shortened by suicide.¹

The first insights into parathyroid function were provided by the French physiologist Eugene Gley at the beginning of the 20th century. He connected the absence of parathyroid glands after thyroid surgery with tetany. In 1907, Jacob Erdheim in Vienna documented that patients who died with osteomalacia and osteitis fibrosa cystica had enlarged parathyroid glands at autopsy. His conclusion that their enlargement resulted from compensatory hyperplasia was erroneous, but his observation was key in making the association between bone disease and abnormalities of the parathyroid glands. In 1903, the first report of a patient with bone disease associated with a large parathyroid tumour was published by Askanazy.

EARLY SURGERY

In 1924, Albert Gahne, a Viennese tram car conductor who had been discharged from the Austrian army with tuberculosis, sustained a fracture of the femur secondary to osteitis fibrosa cystica. Investigations at the Hochenegg Clinic demonstrated elevated blood and urinary calcium levels. Having failed with the use of parathyroid extract, in July 1925, Felix Mandl removed a parathyroid tumour from Gahne's neck, and in doing so performed what is credited to be the first at least initially successful parathyroidectomy.

Gahne's urine cleared within a week, calcium excretion decreased, and the bone pain lessened. A recurrence developed just 6 weeks later –

probably since the original tumour was a parathyroid cancer – and Gahne was re-explored, only to die after the procedure.

Revisionist medical historians (such as the author of this article!) suggest that the first intentional parathyroidectomy was in fact performed at the Middlesex Hospital, London, by Sir John Bland-Sutton (1855–1936) over a decade before Mandl's much quoted operation.² Bland-Sutton was aware of the parathyroid gland and the pathology associated with it, as documented in the sixth edition of his respected textbook *Tumours Innocent and Malignant, their Clinical Characters and Appropriate Treatment* (1917). He described a post mortem specimen of a parathyroid tumour in 1886, surgically removed a parathyroid cyst in 1909, and performed an intentional parathyroidectomy for a parathyroid tumour some time prior to 1917. However, Sir John Bland-Sutton's parathyroidectomy was performed for the mass effect of a large parathyroid tumour, rather than with the intention of curing bone disease.

The earliest recorded parathyroidectomy in the USA was performed by EJ Lewis at Cook County Hospital in Chicago in January 1926, less than 6 months after Felix Mandl's operation. The patient was a 29-year-old woman who, like Gahne, also probably had a parathyroid carcinoma and, also like Gahne, succumbed to the disease.

However, it is the extraordinary documentation surrounding the patient Charles Martell that stands out in medical history. A 30-year-old sea captain, he was transformed by generalised skeletal decalcification. A diagnosis of primary hyperparathyroidism was made at the Bellevue Hospital in New York City in January 1926, and he underwent six unsuccessful neck explorations.

Martell, who, during a long inpatient stay, had read extensively in the Harvard Medical Library about the various locations of the parathyroid glands, insisted that the seventh operation should involve a mediastinal exploration. This was performed by Churchill and Cope at Massachusetts General, and a 3-cm mediastinal tumour

CONTINUED ON PAGE 14...



Sir John Bland-Sutton, pioneer of parathyroidectomy

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ADRENAL SURGERY: ACROSS THE AGES

WRITTEN BY MALCOLM H WHEELER

was found. Unfortunately in the previous six operations all normal parathyroid tissue had been removed, so Captain Martell died of tetanic laryngospasm following surgery to deal with an obstructive uropathy.

EFFECT OF PARATHYROID BIOCHEMISTRY

Berson and Yalow's Nobel Prize-winning development of an immunoassay for the measurement of parathyroid hormone in 1963, combined with the introduction of the serum chemical autoanalyser, dramatically increased the number of diagnoses of primary hyperparathyroidism. However, the surgical and histological expertise was not prepared for this development, and operations took many hours, and were characterised by surgical uncertainty, multiple biopsies, and a high persistence rate and/or hypoparathyroidism rate.

The earlier diagnosis changed the clinical presentation of primary hyperparathyroidism from the aggressive stone and bone disease with gastrointestinal upset and mental illness of the 1950s to paucisymptomatic or even asymptomatic disease in the 1990s. This, and the development of endocrine surgery as a surgical specialty in the 1970s, heralded a new era of parathyroid surgery where surgeons with a dedicated interest in the disease adopted a systematic approach with considerably improved outcomes.

The arrival of reliable pre-operative imaging in the form of high resolution ultrasound and sestamibi scanning in the 1990s changed the face of parathyroid surgery. They were widely adopted despite the 1991 NIH Consensus Statement explicitly expressing that parathyroid localising studies were not cost-effective, and did not improve surgical cure rates or decrease the operating time. They did allow the development of a number of minimal access or targeted surgical approaches in the 1990s, to the point that minimally invasive surgery became the gold standard in localised parathyroid disease, with excellent results that could be further marginally improved with the use of intraoperative parathyroid hormone.

The new techniques, combined with the realisation that 'asymptomatic' hyperparathyroidism may not be innocuous (or indeed asymptomatic), increased the number of parathyroidectomies performed. However, in recent years, the possible increase in long term recurrence following focused parathyroid surgery (perhaps related to a better biochemical detection of recurrent disease) may be driving a return to four gland visualisation, albeit through much smaller incisions by higher volume surgeons.

Perhaps Doppmann's much quoted aphorism from 1986 that 'In my opinion, the only localising study indicated in a patient with untreated hyperparathyroidism is to localise an experienced parathyroid surgeon' may have been right after all.

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Bartholomaeus Eustachius first depicted the adrenal glands in 1552, naming them 'glandulae renibus incumbents', because of their location close to the kidneys. Surprisingly, the early anatomists, including Galen and even Leonardo da Vinci, had overlooked them.

Successive names included 'capsulae suprarenales' (Jean Riolan, Paris, 1629) and 'glandulae renales' (Thomas Wharton, London, 1656). The terms cortex and medulla, to describe the two component parts, were first used by the anatomist and embryologist Emil Huschke, working in Jena, Germany, in 1845.

FUNCTIONAL UNDERSTANDING

The function of the adrenals remained speculative, but in 1855 the Parisian physiologist Claude Bernard proposed that the adrenals produced 'internal secretions'. Coincidentally, in the same year, Thomas Addison described 11 patients showing clinical features of adrenal insufficiency. Autopsy showed adrenal gland disease, destruction or atrophy. Observing death in animals after bilateral adrenalectomy, Charles Edouard Brown-Séquard concluded that the adrenals were essential for life.

But early progress in the understanding of adrenal physiology was slow. At Johns Hopkins University (Baltimore, MD, USA), William Osler made an extract of pig's adrenal which he used in an attempt to treat adrenal insufficiency in 1896, whilst John Jacob Abel isolated epinephrine in 1897.

With limited understanding of adrenal pathophysiology, unsuccessful attempts were made at the Mayo Clinic (Rochester, MN, USA) in 1920 to treat Addison's disease with epinephrine. However, the breakthrough came at the same institution in the late 1930s, when Edward Kendall isolated and later synthesised cortisone. He and Tadeus Reichstein, working independently in Basel, Switzerland, were later awarded the Nobel Prize for their achievements.

Subsequently the biochemistry of the remaining steroid adrenal cortical hormones and the catecholamine hormones of the medulla unfolded, and permitted an understanding of the various syndromes of adrenal endocrine dysfunction. Many of these conditions, especially those associated with excessive hormonal secretion, became amenable to surgical treatment.

SURGICAL MILESTONES AND HORMONE REPLACEMENT

The early key surgical milestones overlapped many of these basic scientific discoveries. Knowsley Thornton (London), who was familiar with the concepts of antisepsis (having been house surgeon to Joseph Lister), performed the first successful adrenalectomy in 1889.

It is thought that no precise preoperative diagnosis of an adrenal tumour was recorded until 1905. Precise preoperative assessment and diagnosis, so crucial to a successful surgical outcome, had to await not just a complete understanding of adrenal biochemistry and reliable hormone assay but also the development of sophisticated localisation techniques, such as cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging, supported by refinements such as selective adrenal venous sampling.



Nevertheless, Kendall's contribution had an immediate impact on adrenal and, later, pituitary procedures. In 1934, before the era of cortisone replacement, Priestley reported a mortality of 30% following adrenalectomy for a variety of pathologies. But once cortisone replacement became available, the same surgeon performed adrenalectomy in 18 cases without mortality.

In 1932, Harvey Cushing demonstrated the pituitary's role in Cushing's disease, but others soon emphasised the key role of the adrenals in the disorder. The treatment of Cushing's disease, whether by pituitary or adrenal surgery, clearly required the availability of corticosteroid replacement for a safe and satisfactory outcome.

Tait and Simpson discovered aldosterone in 1952. This was soon followed by Jerome Conn's description of the syndrome of hyperaldosteronism in 108 hypertensive patients in Ann Arbor (MI, USA) in 1955. Most patients with primary hyperaldosteronism (Conn's syndrome) are now treated by unilateral adrenalectomy.

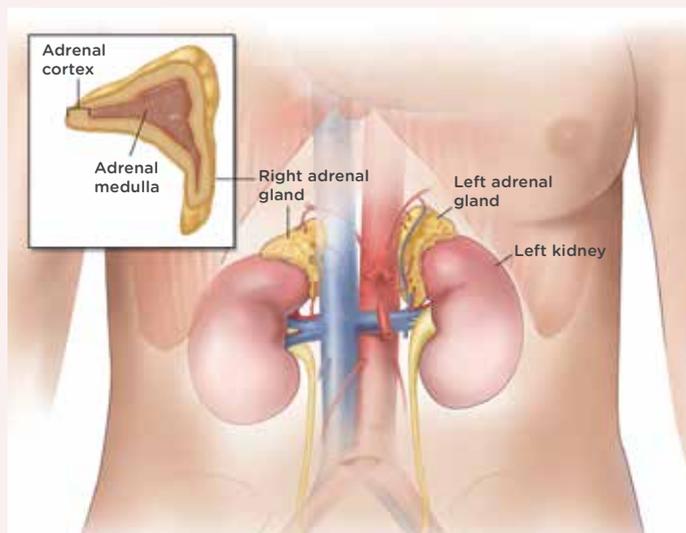
PHAECHROMOCYTOMA AND MEN

Excessive hormone secretion by the adrenal medulla results in the dramatic condition of phaeochromocytoma. After biochemical confirmation and localisation, patients are medically prepared by adrenergic blockade and then treated by adrenalectomy. One of the fascinating features of this tumour is its frequent (up to 25%) occurrence in familial form, as part of a genetically inherited disorder such as multiple endocrine neoplasia (MEN IIa, IIb) von Hippel-Lindau disease, neurofibromatosis 1 and succinate dehydrogenase (SDHD) gene mutations.

Medullary thyroid carcinoma is the dominant clinical feature in the MEN II syndromes, with phaeochromocytoma developing in up to 50% of cases. The genetic abnormality in MEN II has been identified as a single point mutation and amino acid substitution in the *RET* proto-oncogene on chromosome 10. This finding has permitted genetic analysis and identification of family members at risk of developing MEN II and has led to the introduction of 'prophylactic thyroidectomy' for gene mutation carriers.

Anatomy of the adrenal gland

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SURGICAL APPROACHES

Because of the adrenals' relatively inaccessible anatomic location, surgery has often been challenging. Most early adrenalectomies were performed for large tumours and required large incisions. These incisions were similar to those used for renal surgery, but were frequently too low to permit adequate and safe adrenal access. Surgeons began to site their incisions at higher levels, usually resecting the 11th or 12th rib.

Various anterior, lateral and retroperitoneal approaches became established, each with their own merits and problems. Anterior incisions permitted a full exploration of the abdomen and the ability to deal with bilateral adrenal pathology, but such wounds were often painful and slow to heal, especially in Cushing's patients.

A posterior approach removing the 12th rib was popularised by Young (Baltimore, MD, USA) and was ideal for the removal of small tumours such as a Conn's adenoma, but proved inadequate for lesions over 5cm in diameter.

Open surgical access to the adrenal remained unchallenged until 1992, when Gagner (Montréal, Canada) described a minimally invasive approach. This technique, utilising a transperitoneal or retroperitoneal approach, soon became the new 'gold standard', conferring very real advantages for the patient, especially those with hypercortisolism. At a stroke, the disadvantages of large, painful, cosmetically unsatisfactory incisions, slow recovery and lengthy hospitalisation were markedly reduced.

Currently, evidence favours minimally invasive surgery for small, benign, functioning and non-functioning adrenal lesions. Laparoscopic techniques are generally not considered suitable for large, malignant or potentially malignant tumours.

AUGMENTED AND VIRTUAL REALITY

Such techniques have paved the way for even more spectacular developments - namely the field of augmented and virtual reality pioneered by Jacques Marescaux in Strasbourg, France.

Creation of an augmented image from 2mm slice CT allows the surgeon to identify preoperatively the precise details and difficulties (for example, abnormal anatomy) of a planned procedure, and to manipulate and navigate the image and even to rehearse the operation the day before.

During surgery the real and virtual images are superimposed, serving as a roadmap and providing a degree of surgical safety hitherto only dreamt of. This technology also clearly has enormous training potential.

The adrenal story is a fascinating one with respect to the understanding of anatomy, physiology and pathology, utilisation of sophisticated diagnostic methods and evolution of an exciting surgical technique. Many challenges remain, especially regarding the investigation and management of inherited disease and the application of procedures such as subtotal adrenalectomy to preserve natural cortical function, obviating the need for cortisol replacement.

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COMPETENCY FRAMEWORK FOR ADULT ENDOCRINE NURSING - 2ND EDITION

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Kieffer V *et al.*, 2015. Society for Endocrinology Competency Framework for Adult Endocrine Nursing: 2nd edition. *Endocrine Connections* 4 W1–W17. (doi:10.1530/EC-14-0134)

<http://www.endocrineconnections.com/>



HISTORICAL IMAGES IN ENDOCRINOLOGY

For your interest, here are some selected images from the endocrine archives, which simply didn't fit elsewhere.



The pancreas and the pancreatic duct (engraving after JG Wirsung, 1644) ©Wellcome Library, London



Bronze female statue showing a goitre growth (Nigeria, 19th century) ©Science Museum London, Wellcome Images



Advert for Lydia E Pinkham's 'Vegetable Compound', which was used for all female complaints, including menstrual and menopausal pains (1880s) ©Wellcome Library, London



Case VI Before Insulin



Case VI 4 Mos. After



Cartoon of Ernest Starling, who first coined the term 'hormone', taken from the *UCL Gazette* ©Wellcome Library, London

Young girl before and after insulin treatment (from Geyelin 1922 *Journal of Metabolic Research* 2 5-6) ©Wellcome Library, London



Ivory anatomical female figures (date unknown), with body panel removed to reveal organs beneath ©Wellcome Library, London

THE THYROID: THEN AND NOW

WRITTEN BY MICHAEL SHEPPARD



As long ago as 1600 BCE, the Chinese made use of burnt sponge and seaweed as a therapy for goitres, while in about 1500 BCE Indian texts mention goitre as 'galaganda', and describe its treatment. Moving forwards a few millennia, the Roman writer Celsus first described a bronchocele (tumour of the neck) in 15 CE. Slightly later still, Pliny commented on goitre epidemics and the therapeutic use of burnt seaweed. In 150 CE, Galen too suggested 'spongia usta' (burnt sponge) for goitre.

So it is that we encounter very early references to thyroid medicine. However, the thyroid gland was not described anatomically until 1475, when Chinese physician Wang Hei recommended its treatment with dried thyroid. Half a century later, the Swiss scholar Paracelsus suggested a link between goitre and mineral impurities in water. One of the earliest references to the thyroid in Western medicine dates from 1656, when it was identified by the English anatomist Thomas Wharton. Wharton gave the thyroid its name, from the Greek 'thyreos', as its shape was reminiscent of the shields depicted in Ancient Greece.

ELUCIDATING THYROID FUNCTION

Numerous suggestions were made regarding the thyroid's function, such as lubrication of the trachea, diversion of blood from the brain or a cosmetic role in females. In 1820, Rush explained the larger thyroid gland in women as being 'necessary to guard the female system from the influence of the more numerous causes of irritation and vexation of mind to which they are exposed than the male sex.' In the same year, Hofrichter commented 'Husbands would have learned to recognise the swelling of this gland as a danger signal of threatening trouble from their better halves'!

With regard to diseases of the thyroid, cretinism was first described in 1871. In 1894, Gull recorded the clinical changes seen in thyroid atrophy and Ord adopted the term myxoedema, because he thought the characteristic thickening of subcutaneous tissue was caused by excessive mucus formation and deposition under the skin.

Theodore Kocher
©Wellcome Images,
London

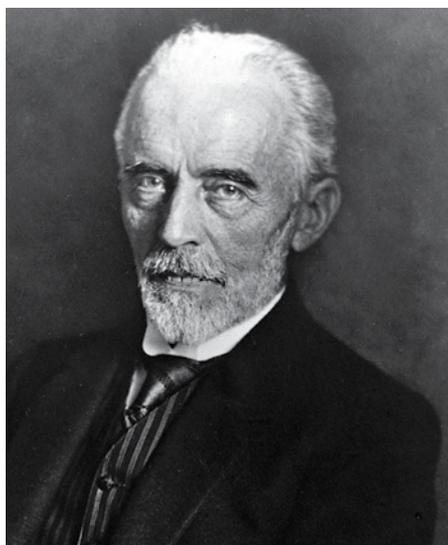


Illustration of the thyroid gland ©123 RF Stock

In 1891, Murray noted a good clinical response in hypothyroidism by injecting patients with sheep thyroid extracts. During the 19th century, Coindet, an Edinburgh-trained physician working in Geneva, successfully treated goitres with iodine.

Thyroidectomies were successfully undertaken in 1884 for treatment of toxic goitre. In Europe, Swiss surgeon Theodore Kocher performed over 2,000 thyroidectomies with a reported mortality rate of 5%. He was rewarded in 1909 with the Nobel Prize in Physiology or Medicine 'for his work on the physiology, pathology and surgery of the thyroid gland'. Meanwhile, in the USA, Charles Horace Mayo became an authority on thyroid surgery. By the 1920s, thyroid surgery was commonplace.

UNDERSTANDING THYROID HORMONES

It was in the 20th century that the thyroid's secretion of an iodine-containing substance was examined. In 1914, Edward Kendall, Professor of Physiological Chemistry at the Mayo Clinic (Rochester, MN, USA), isolated crystalline thyroxine (T_4). He found it had the same effects as the thyroid extract from which it came. More than a decade later, in London in 1926, Harrington defined the chemical formula of T_4 , and subsequently synthesised the hormone. The ability to synthesise sodium L-thyroxine, and the fact that it could be absorbed orally, made thyroid replacement safe and cheap. The calorogenic effect of synthetic T_4 was less than that of thyroid extracts, however. This enigma was not resolved until 1952, when Rosalind Pitt-Rivers and her post-doctoral fellow Jack Gross discovered and synthesised tri-iodothyronine (T_3), and proved it was biologically more active than T_4 .

HYPERTHYROIDISM

It was not until 1786 that the link was made between thyroid enlargement and the clinical appearance of hyperthyroidism. It was noted by Parry, a provincial physician in Bath, but he did not publish his observations until 1825. This publication was followed by the classic descriptions by Graves and von Basedow in 1835 and 1840 respectively.

Robert Graves (1796–1853) is primarily remembered for his clinical description of Graves' disease of the thyroid gland. In 1834 at the Meath Hospital, Dublin, he remarked 'I have lately seen three cases of violent and long continued palpitations in females, in each of which the same peculiarity presented itself - viz. enlargement of the thyroid gland; the size of this gland, at all times greater than natural ... A lady aged 20 became affected with some symptoms which were supposed to be hysterical ... it was observed that her pulse had become singularly

rapid ... began to look pale and thin ... the eyeballs were apparently enlarged, so that when she slept or tried to shut her eyes, the lids were incapable of closing.' He concluded that these phenomena were all linked in a single condition.

Von Basedow also described many of the main features of hyperthyroidism but, although his work was contemporaneous with that of Graves, he did not publish until 5 years later. Despite this, the disease is referred to as Basedow's disease in many non-English speaking countries.

There is little doubt that Parry was the first to describe the disorder – but why is it so widely termed Graves' disease? It is reported that Graves attracted the unbidden services of an excellent French publicist, who advanced the Irishman's cause in preference to that of the Englishman!

HYPOTHYROIDISM

The Japanese physician Hakuru Hashimoto (1881–1934) from Kyoto first described the symptoms of 'struma lymphomatosa' in 1912. Known as Hashimoto's thyroiditis, this autoimmune condition sees infiltration of lymphocytes into the thyroid. His paper discussed the results of his examination of thyroid tissue samples taken from four women with a chronic disorder of the thyroid presenting with a painless, diffuse enlargement of the thyroid gland, often associated with hypothyroidism.

Overt thyroid dysfunction is recognised today as common in the general population, with a prevalence of thyrotoxicosis or hypothyroidism of at least 2% in females and 0.2% in males in the UK. The diagnosis of many of these conditions is relatively simple, particularly with the introduction of techniques for the measurement of circulating free hormone and assays for thyrotrophin (TSH) with increased sensitivity. The prognosis is excellent if managed in a timely manner. Neonatal screening programmes for hypothyroidism are now the standard of care, and have shown an incidence of 1 in 3,500–4,500 births.

Subclinical thyroid dysfunction, defined as serum TSH levels outside the normal reference range with normal levels of free T_4 and free T_3 , is even more common, with estimates ranging from 2.2 to 11.6%. There is much debate about the significance of mild abnormalities of thyroid function in terms of symptoms and potential associations with long term morbidity and mortality. Hence there are also many discussions about whether to screen for these abnormalities and, once identified, whether and how to treat or monitor them.

LEAPS AND BOUNDS

The last 60 years have seen many landmarks in our understanding of thyroid disease. In the 1950s, thyroid-stimulating antibodies were identified in Graves' disease and thyroid antibodies in Hashimoto's disease, and medullary thyroid carcinoma was recognised. Calcitonin's discovery in 1961 shone light on the gland's role in calcium metabolism, while resistance to thyroid hormone was described in 1967.

As the 1970s dawned, so came understanding that circulating T_3 is produced in the main by peripheral monodeiodination of T_4 ; this was followed by identification of the T_3 -binding receptors. The middle of the decade saw description of postpartum thyroiditis with hypothyroidism or thyrotoxicosis.

By the late 1980s, it became clear that point mutations in the thyroid hormone receptor accounted for hormone resistance. After the TSH receptor gene was cloned, it was shown that loss- and gain-of-function

mutations in that receptor account for specific types of hypothyroidism and hyperthyroidism.

THYROID CANCER

The Chernobyl nuclear reactor accident in 1986 was a devastating event, and brought to the attention of the world the relationship between thyroid cancer and radioactive iodine. It has been calculated that 5,000–10,000 thyroid cancers have occurred in children and adolescents who were exposed to radioiodine at the time of the accident. Although these figures have been disputed, it is likely that a large fraction of these cancers is attributable to radioiodine intake.

Thyroid enlargement affects around 15% of the population, but thyroid cancer is rare, so the challenge is to identify the few patients with neoplastic disease. The estimated prevalence of thyroid nodules on the basis of palpation ranges from 3 to 7%. During the past two decades, according to widespread use of ultrasonography, the prevalence of clinically unapparent thyroid nodules has increased, and is estimated at 20–76% in the general population. This makes the differentiation from benign, insignificant disease even more problematic.



Hakuru Hashimoto
©Wellcome Images,
London

IN CONCLUSION

The study of the thyroid is a remarkable story of scientific discovery, application to human disease and immense therapeutic benefit. The unanswered questions regarding thyroid disorders still exercise the minds of researchers, but additional clinical benefits may be marginal. Such issues include the relevance of subclinical thyroid dysfunction and small thyroid nodules, the benefits of stimulated thyroglobulin versus suppressed thyroglobulin levels in the presence of suppressive doses of T_4 , the long term risks of suppressive T_4 therapy in thyroid cancer, and advantages of thyroid extract over T_4 replacement.

Are there any more eponymous diseases to be recognised which have significant clinical impact? Probably not. As my mentor, the late Bill Hoffenberg, used to say to me on a regular basis, 'Any advance on thyroxine and radioiodine?'

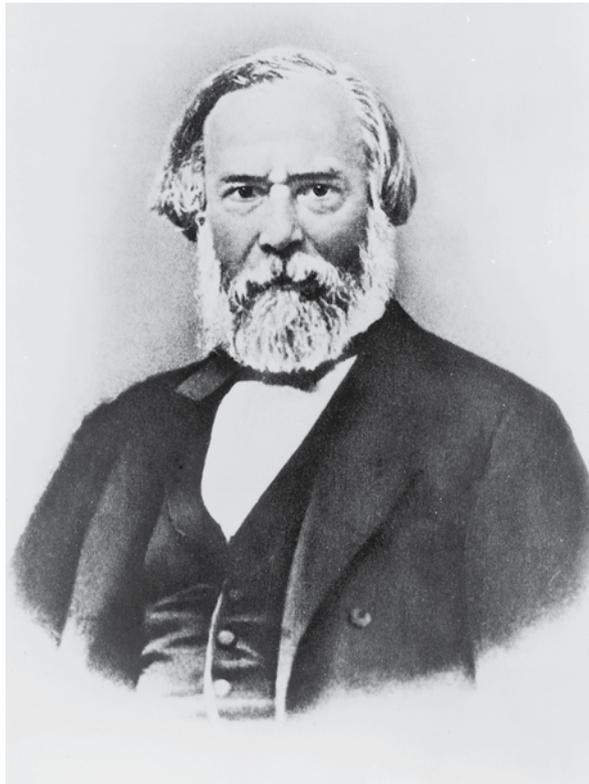
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MILESTONES IN THE HISTORY OF HRT

WRITTEN BY SAFFRON WHITEHEAD



The story of hormone replacement therapy (HRT) begins in 1889 when, at the age of 72, Charles Edouard Brown-Séquard reported to the Société de Biologie in Paris the invigorating effects of injecting himself eight times with an aqueous extract of dogs' testicles. He attributed this effect to an action on the nervous system and suggested that similar extracts could be used to rejuvenate men.



Charles Edouard Brown-Séquard
©Wellcome Images, London

A few weeks later, the *British Medical Journal* published an editorial entitled 'The pentacle of rejuvenescence', indicating the unsettling nature of these claims. Britain viewed Brown-Séquard's results with caution, whilst Americans referred to it as 'the elixir of life'.

A year later, Brown-Séquard reported that an American woman, Augusta Brown, had injected several women with filtered juice of guinea pigs' ovaries, so benefiting hysteria, uterine afflictions and ageing debility. This claim could not be validated, but in 1896 the first of several papers about the successful use of ovarian extracts in the Landau Clinic in Berlin was published.

THE ERA OF ORGANOOTHERAPY

Brown-Séquard's naïve experiment led to the era of organotherapy, in which a plethora of animal extracts, including glands, were used as therapeutic agents. Organotherapy remained a contentious issue for over 30 years, although it did reach some degree of respectability in 1891 after George Redmayne Murray's success in treating myxoedema (hypothyroidism) with extracts of thyroid glands.

The pharmaceutical companies had been quick to jump on the organotherapy bandwagon and this included production of a wide range of watery ovarian extracts, such as 'ovarine oophorin', with dubious, if any, biological activity. It was not until 1912 that it was discovered that the 'active principle' in the ovaries could only be extracted using lipid solvents. Unlike watery extracts, the lipid

extracts could have striking effects on the uterus when tested in the laboratory. Soon the practice of organotherapy came under attack by scientists.

DISCOVERY OF OESTROGENS

In 1923 Edgar Allen and Edward Doisy partially purified an oestrogenic hormone from pigs' follicular fluid, and in 1927 Bernhard Aschheim and Selmar Zondek discovered that the urine of pregnant women contained a highly oestrogenic substance. This led to the isolation of pure crystalline oestrone by Doisy and colleagues in 1929, followed by progesterone in 1934, oestradiol in 1935 and testosterone in 1939. In 1930, Zondek showed that oestrogens could be produced from pregnant mares' urine.

These water-soluble oestrogens were subsequently found to be conjugated with acid or sulphate, and extracts of these conjugated oestrogens were put on the market as orally active oestrogen preparations. In 1938, ethinyl oestradiol was synthesised and the first potent synthetic steroid, diethylstilboestrol, was discovered – both are long acting and highly active oestrogens.



'Progynon' was a 'hormone supplement' used to treat the effects of the female menopause. It first appeared on the market in Germany in 1928.

To make the pills more affordable, the hormone extract was obtained from the urine of pregnant women.

©Science Museum London, Wellcome Images

TABLE 1. FINDINGS OF THE WOMEN'S HEALTH INITIATIVE AND MILLION WOMEN STUDY

OESTROGEN PLUS PROGESTERONE		OESTROGEN ALONE	
	Risk of: breast cancer stroke blood clots		Effects on: breast cancer
	Risk of: bowel cancer osteoporosis		Risk of: stroke blood clots
			Risk of: bowel cancer
			Risk of: fractures

THE RISE OF MENOPAUSAL OESTROGEN THERAPY

Initially, oral and injectable oestrogens were marketed for the treatment of menstrual irregularities. However, by the early 1930s, reports of their use for treating menopausal symptoms began to appear. The index for their success was evaluated in terms of the reduction of hot flushes rather than other associated symptoms of the climacteric. By the end of the 1930s, the American gynaecologist Emil Novak wrote '...the efficacy of oestrogenic therapy is clearly to be explained by the undoubted physiological potency of these preparations... Contrast this with the uncertainty of ovarian therapy before the isolation of the oestrogenic hormone'.

The UK lagged behind America in prescribing oestrogen replacement therapy, but opening menopause clinics helped to raise the profile of the menopause amongst non-specialist GPs and women. Widespread publicity was driven by the publication of Robert Wilson's popular and polemic book, *Feminine Forever* in 1966.

This American gynaecologist argued that menopausal women were castrates suffering from a deficiency disease; 'The transformation within a few years of a formerly pleasant energetic woman into a dull-minded but sharp-tongued caricature of her former self is one of the saddest of human spectacles.' He argued that all women should take oestrogen therapy to keep them young and sexually active. The book sold 100,000 copies within 7 months of publication.

Widespread publicity in the UK was to come later, and has often been attributed to Wendy Cooper's journalistic profile and publication of her book *No Change* in 1975.

HRT CONTROVERSIES

This was the same year that the rumbling controversy over oestrogens and risks of breast and uterine cancer erupted. Donald Smith and colleagues published the first epidemiological evidence of an increased risk of carcinoma amongst oestrogen users. By 1980, 14 studies on oestrogen replacement therapy and endometrial cancer had been published, seven in *New England Journal of Medicine*.

Prescriptions of oestrogen therapy dropped dramatically and so pharmaceutical companies promoted the use of combined oestrogen/progestagen preparations to induce a bleed and reduce risks of uterine hyperplasia. The combined hormone preparations became generally known as HRT. Edmund Novak (Emil's son, also a gynaecologist) stated, 'What 60-year-old woman needs continued menstruation as a badge of femininity?'

The second response of the pharmaceutical companies was to promote extended use of HRT for the prevention of osteoporosis (in particular) and cardiovascular disease, but not all doctors agreed with its long term use.

The prescribing of HRT saw a further major setback in the early 2000s after the publication of research from the USA's Women's Health Initiative (WHI) and the UK's Million Women Study (MWS), reporting observed risks and benefits of HRT (summarised in Table 1). There was widespread coverage in the press. A quote from *The Observer* in 2002 summed it up in a nutshell: 'Damning study on HRT leaves women in limbo. The startling news that HRT may do more harm than good has caused worldwide confusion and panic. Where do the answers lie?'

Prescriptions of HRT dropped by up to 50% in some countries. Results of the studies were subsequently reanalysed and concerns about their conclusions arose. By 2011, the fourth MWS report concluded that the risk of breast cancer reverts to levels of non-users 2 years after stopping HRT. Today, long-term hormone replacement therapy is no longer advised and should only be used to treat menopausal symptoms, not for any extended health benefits it may have.

So no longer 'feminine forever' or do our social constructs and increasing longevity in the Western world now allow oestrogen deprived post-menopausal women to live healthy and normal lives without HRT? Meanwhile we remain in limbo, and the rocky road of the history of HRT continues.

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THE MAKING OF TESTOSTERONE

WRITTEN BY EBERHARD NIESCHLAG AND SUSAN NIESCHLAG



Removal and transplantation of endocrine glands are among the earliest tools in experimental endocrinology. The testes, with their exposed position, are vulnerable and easily accessible for external manipulation, including trauma and forceful removal. Thus, the effects of testosterone and its absence, resulting from loss of the testes, became evident quite early in history, while the actual substance responsible for these effects was identified only 80 years ago.

EFFECTS OF TESTIS REMOVAL

Castration has been used to produce obedient slaves, loyal to their masters and rulers. Over the centuries in Islamic societies, castrated slaves formed elite troops deployed in wars of conquest. At the Chinese imperial court, documented since the Ming dynasty, eunuchs obtained high-ranking positions. This is exemplified by Admiral Zhèng Hé (1371–1435), leader of seven large expeditions into countries around the Indian and Pacific Oceans, or Lin Yin (1451–1510), who is still counted among the richest people in history. The last imperial eunuch, Sun Yaoting, died in 1996 at the age of 94.

Castration has also been used as lawful punishment. In Scandinavia, high treason was not subject to capital punishment, but to castration combined with blinding. This was adopted by the Normans, who introduced this legislation wherever they ruled. After the Norman Conquest of England in 1066, William the Conqueror abolished the Anglo-Saxon death penalty and replaced it with castration and blinding: 'I also forbid that anyone shall be slain or hanged for any fault, but let his eyes be put out and let him be castrated.'

Prepubertal castration maintains the high voice of boys, resulting in soprano and alto voices with the acoustic volume of an adult male. These featured in operas in the 17th and 18th centuries. In the Vatican choirs, these voices could be heard until the early 20th century. Some of these castrates became famous soloists, such as Farinelli (1705–1782) and Domenico Annibaldi (1705–1779). The central Italian cities of Norcia and Preci specialised in surgery on young boys, going back as far as the 13th century, and the 30 family dynasties that monopolised the trade there guaranteed utmost secrecy concerning this illegal operation.

LESSONS FROM EXPERIMENTAL TESTIS TRANSPLANTATION

While removal of endocrine glands is one basic tool in experimental endocrinology, replacing glands is the other. As a surgeon in the Seven Years' War (1756–1763), John Hunter (1728–1793) saw the need for transplantation of organs and limbs, and this stimulated his experiments involving transplantation of testes from cocks to hens, thereby demonstrating the 'vital principle' of living organs. Far from any endocrine thought, his goal was to demonstrate the survival of the transplant due to nerve growth.

In Göttingen, Arnold Adolph Berthold (1803–1861) also used the chicken as an experimental model. He observed that testes transplanted from roosters to capons restored androgenic functions and concluded

that these effects 'must be affected through the productive relationship of the testes, that is to say, through their action on the blood, and then through the suitable ensuing action of the blood on the organism as a whole' (1849). He was thus the first to postulate a humoral effect of the testes on distant organs.

ON THE WRONG TRACK: ORGANO THERAPY

Berthold's unique discovery was superseded by organotherapy, which exploded after Charles Edouard Brown-Séquard (1817–1894) published the results of his dubious self-experimentation in *The Lancet* in 1889. He self-injected a mixture of testicular vein blood, semen and juice extracted from dog or guinea pig testes and observed signs of rejuvenation. These at best must have been placebo effects, since the testes synthesise testosterone, but do not store it, and the amount administered was minute. However, in no time the 'extracts of animal organs by the Brown-Séquard method' were sold worldwide and factories sprang forth in Europe as well as in America. The craze for these products caused concern about the image of the young field of endocrinology. The famous neurosurgeon Harvey Cushing (1869–1939) even talked about 'endocrinology' in the context of this organotherapy.

ARRIVAL OF TESTOSTERONE

Despite the impact of organotherapy, Berthold's discovery was not permanently forgotten, as several scientists – among them Albert Pézard in Paris in 1912 – confirmed Berthold's observations and the search for the androgenic substance in the testes began. Various drug companies co-operated with scientists in order to replace the discredited organotherapy with proper hormone substitution.

In 1931, Adolf Butenandt isolated the androgenic steroid androsterone (androstan-3 α -ol-17-one) from 15,000 litres of urine provided by young policemen from Berlin, which was then processed by Schering AG to obtain 15mg of this first androgen. In 1935, Ernst Laqueur (1880–1947) and his group in Amsterdam extracted and isolated 10mg of testosterone (androsten-17 α -ol-3-one) from 100kg of bull testes. They found this to be more active than androsterone and named it 'testosterone'. In the same year, Adolf Butenandt and Günter Hanisch in Göttingen, as well as Leopold Ruzicka and A Wettstein in Basel, published the chemical

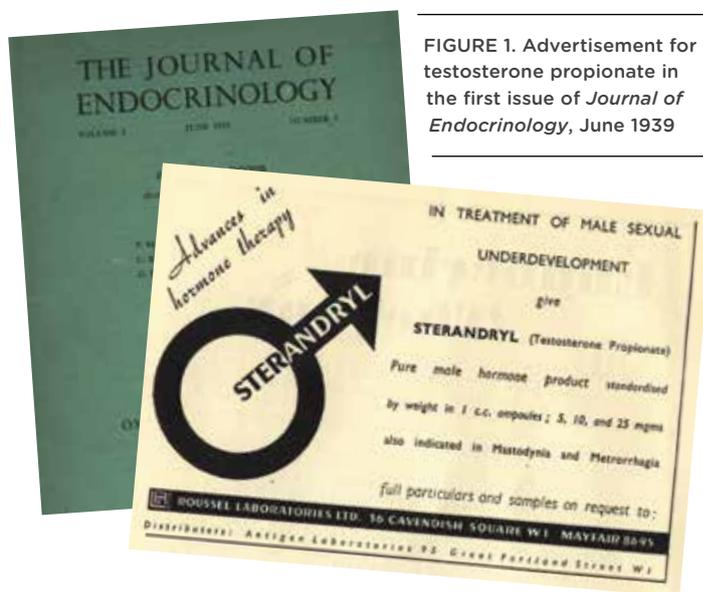


FIGURE 1. Advertisement for testosterone propionate in the first issue of *Journal of Endocrinology*, June 1939

'The effects of testosterone and its absence, resulting from loss of the testes, became evident quite early in history, while the actual substance responsible for these effects was identified only 80 years ago.'

synthesis of testosterone, marking the beginning of the modern clinical pharmacology of testosterone and male reproductive physiology.

TESTOSTERONE PREPARATIONS FOR CLINICAL USE

Soon after its synthesis, testosterone became clinically available, first as pellets and then as injectable esters, i.e. **testosterone propionate** with a short half-life (Figure 1) and, from the mid-1950s onwards, the longer-acting **testosterone enanthate**. This provides substitution for 2–3 weeks and remained the major testosterone preparation for half a century.

Also, in 1935, **17 α -methyl-testosterone** was synthesised, and its oral effectiveness was demonstrated. However, due to its 17 α -structure, it was hepatotoxic, thus giving testosterone in general a bad name among physicians. Eventually, in the 1980s, this androgen became obsolete for clinical use – at least in Europe.

The late 1970s saw the **orally effective testosterone undecanoate**, absorbed from the gut via the lymph to avoid the first-pass effect in the liver. After initial clinical testing in our group¹, it was added to the spectrum of testosterone preparations available for replacement therapy.

In the 1950s and 1960s, instead of improving modes of application, the pharmaceutical industry became more interested in the chemical modification of the testosterone molecule, in order to disentangle its various effects and produce predominantly erythropoietic or anabolic steroids. Although hundreds of androgens were synthesised, it proved impossible to produce androgens with only *one* desired effect out of the wide spectrum of testosterone's activities. Nevertheless, while some **anabolic androgenic steroids** were used clinically, they disappeared again in the wake of evidence-based medicine. However, they retained a shadowy existence for doping in sports and body-building, potentially causing considerable undesired effects.

Regrettably, at that time, the pharmaceutical industry ignored the needs of hypogonadal patients, as pharmacokinetic studies had revealed that the existing testosterone preparations resulted in unphysiologically high or low serum levels, undesirable for substitution purposes.

In the mid-1990s, **transdermal testosterone patches** applied to the *scrotal* skin became the first transdermal testosterone preparation in clinical use. Invented by Virgil Place (1924–2012; Figure 2) at Alza in Palo Alto, California, and first tested by us, they showed excellent results, as published in *The Lancet*.² For the first time, physiological testosterone serum levels could be achieved.

However, physicians were reluctant to prescribe a medication to be applied to the scrotum, preferring a subsequently developed **non-scrotal system**. This, however, caused unpleasant skin reactions, as it required an enhancer to drive testosterone through the skin. For this

reason, the advent of the first **transdermal testosterone gel** in 2000 was welcomed for substitution. Of the various gels available, the one with the highest testosterone concentration (2.5% Testotop®) has also been tested³ (but not licenced) for scrotal application. Because of the high absorptive capacity of scrotal skin, only 20% of the gel needed for non-scrotal application is required, making this form of application economically and ecologically more desirable.

Finally, in 2004, the **intramuscular testosterone undecanoate** preparation entered the market and soon achieved great popularity as a real testosterone depot preparation. Testosterone undecanoate, originally used in oral capsules (as mentioned above), had been turned into an injectable preparation by Chinese investigators using tea seed oil as a vehicle. When we came across it at a meeting in Beijing in 1993, samples were brought to Germany, injected into monkeys and showed a surprisingly long half-life. This could be confirmed in hypogonadal male volunteers, who all showed serum levels in the normal range for several weeks.



FIGURE 2. Pua Mau Botanical Garden (Hawaii) established by Virgil Place, inventor of the first transdermal testosterone preparation and later of MUSE[®] for treatment of erectile dysfunction

When a company finally became interested in this fascinating preparation, tea seed oil was replaced with castor oil as vehicle, and the injection intervals were extended to 12 weeks of physiological serum testosterone levels. Today, this preparation has been licensed as Nebido[®] or Reandron[®] in over 100 countries. The latest approval came for Aved[®] from the US Food and Drug Administration in 2014.

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A THRIVING SOCIETY: NO TIME TO STAND STILL



WRITTEN BY STEPHEN BLOOM

'The idea of launching a Journal of Endocrinology and, as a follow-up, to found a Society for Endocrinology, was conceived in a bus going to Croydon Airport on 9 June 1937. Those concerned were Sir Charles Dodds Bart FRS, Sir Frank Young FRS, Sir Alan Parkes FRS, and myself. The four of us were on our way to Paris to attend the Singer–Polignac Colloque, the first international symposium on the physiology of reproduction ever to be organized ...

I do not know whether or not we had all seriously thought before the bus-ride of the desirability of taking the step we ultimately took. But I had. I well remember the sense of frustration I experienced in those days with the delays in the publication of papers. We were then in the heyday of the growth of endocrinology, and of reproductive physiology in particular. Almost any experiment seemed to produce fascinating results. I had come firmly to believe that endocrinology deserved to be recognized both by a British Society and by its own Journal.'

SOLLY ZUCKERMAN (BARON ZUCKERMAN OM KCB FRS), WRITING IN THE 100TH VOLUME OF JOURNAL OF ENDOCRINOLOGY (1984 100 1-6)

The Society is almost 70 years old. When it was established, we knew exactly what endocrinology meant. The discipline then focused on the classical glands: pituitary, adrenal, thyroid etc. Simply removing these glands was often the prescribed treatment. Nowadays, with discoveries such as the complexity of the steroid family and intracellular messaging, endocrinology is no longer quite as well defined as it once was. Endocrinology is taking over the world!

ENDOCRINE REVOLUTION

This rings true in my own field. Gut hormones come from endocrine cells scattered in the bowel mucosa, and were not really thought of as important. It wasn't until glucagon-like peptide-1 (GLP-1) was found to have insulin-releasing action that these hormones were more readily welcomed into the endocrine camp. GLP-1 is now the fastest growing diabetic therapeutic, also being introduced to treat obesity!

This isn't the only expansion of understanding. Cytokines and neurotransmitters are also chemical signalling molecules, but not traditionally thought of as part of endocrinology. They are widely used as control systems to modify disease. Thus the boundaries of the discipline are expanding massively, and endocrinologists suddenly have their fingers in many pies. Some of them don't even call themselves endocrinologists - including members of my own lab! It begs the question: what is endocrinology? Perhaps the discipline of understanding control systems?

New hormones are being discovered all the time. Treatment with the aptly named kisspeptin has allowed women with infertility to safely conceive children. Anti-tumour necrosis factor molecules are being used in Crohn's disease. Interleukin-17 antibodies are undergoing amazingly successful phase III trials in psoriasis, a horrible disease with many sufferers. It is undeniable that endocrinologists, with their knowledge of control mechanisms, have a key role to play.

AN EVOLVING ROLE

The question is how can the Society for Endocrinology support this discipline as it becomes larger, more pluralistic and more important? The Society's original remit was to provide a platform for experts to disseminate knowledge efficiently, so patients could benefit from the latest findings. These days, with many communication channels at our disposal, and the abundance of accessible information online, this purpose may be becoming relatively less important.

The Society has successfully reflected the increasing diversification of endocrinology. For example, this can be seen in the scientific programmes at the annual SfE BES conference and other training events. We now have sessions on gut endocrinology and neuroendocrinology among many other interdisciplinary subjects. Introduction of new journals over the last 30 years covering molecular endocrinology, cancer and other topics has provided ever-expanding platforms for new travellers on the endocrine journey.

This evolution has only been possible because the members remain at the centre of our Society, steering its course and shaping its future.

MEETING HUMAN NEEDS

However, the Society for Endocrinology is and will remain a social platform. Human beings rather like seeing and talking to one other. The Society is an important place for young researchers to present their work to peers and a forum for building networks (personal and professional!) with like-minded scientists, clinicians and specialist nurses.

Indeed, my own experiences are testimony to this. I met a future collaborator from the Karolinska Institute at a Society conference (gosh, 44 years ago!). This was the start of an important collaboration and my life's work, establishing a major international endocrine laboratory.

Supporting and enhancing the careers of endocrinologists remains an ongoing success for the Society and will ensure its prosperity. We must help people identify themselves with our ever-evolving discipline. Curiously, we discover the Society is actually about people meeting people - fighting, getting jealous, becoming infatuated - anything which motivates new learning and new discoveries. We aim to use this human dimension to understand disease and to make the world a better place.

STEPHEN BLOOM

*Division of Diabetes, Endocrinology and Metabolism,
Hammersmith Hospital and Imperial College London*

Stephen Bloom will receive the Society's Jubilee Medal in 2016, to mark the Society's platinum (70th) anniversary. The Jubilee Medal is an occasional award, made by Council to an endocrinologist in recognition of their outstanding contribution to endocrinology and to the Society.



SfE BES

2-4 November
EDINBURGH

2015

KEY DATES

Abstract deadline:

15 JUNE 2015

Early-bird registration
deadline:

**21 SEPTEMBER
2015**

**SAVE
THE DATE**



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**Society for
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Prof D W Ray



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New Clinical Endocrinology Trust funding for quality improvement projects

The Clinical Endocrinology Trust has long supported endocrine audit projects in the UK. Recent examples include:

- the UK Acromegaly Register
- the CaHASE audit of adults with congenital adrenal hyperplasia
- the national audit of cabergoline and valvulopathy
- the British Thyroid Association study of UK teenage iodine status

The Trustees now invite further applications from societies or endocrine centres, with preference given to multicentre collaborations. Applications are particularly welcome if they relate to areas of endocrinology that the Trust has not previously supported.

A total of £50,000 is available during 2015–2016 for a number of projects that the Trustees judge to be worthy of support. Previously, approximately £10,000–20,000 has been awarded per project. The closing date is 30 June 2015.

The decision of the Trustees will be final. Projects must commence within 6 months of an award being made. An abstract describing the outcome of the supported project must be submitted to the Society for Endocrinology BES conference within 24 months of the award.

Applications should be sent to Dr SG Ball, The Endocrine Unit, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP (Email: S.G.Ball@newcastle.ac.uk).

We look forward to hearing from you!

The Clinical Endocrinology Trust is a charity deriving its income from a profit-share of the Society for Endocrinology's official clinical journal, *Clinical Endocrinology*.

ENDOKININ: THE PLACENTAL TACHYKININ BEHIND MORNING SICKNESS?

WRITTEN BY PHIL LOWRY



The physiological rationale for the placenta expressing and translating many neuropeptide genes into polypeptides has puzzled me for many years. Those we studied have all been found to carry a post-translational modification (PTM) containing phosphocholine, either on the processed peptide (neurokinin B, NKB)¹ or on the precursor (procorticotrophin-releasing factor, proCRF).²

Placental NKB reaches concentrations in the maternal blood that could cause many of the symptoms of pre-eclampsia,³ and CRF stimulates the pituitary-adrenal axis when its binding protein levels decline 3 weeks before parturition.⁴ There is, however, little evidence for other placentally produced peptides influencing the mother's physiology.

Certain filarial nematodes avoid host rejection by secreting a phosphocholinated protein which has immune-attenuating properties.⁵ Thus it is possible that the placenta achieves the same end by secreting small amounts of many phosphocholinated placental peptides (individually not high enough to have any physiological effect), such that the total phosphocholinated peptide activity reaches concentrations sufficient to attenuate the mother's immune system.

It is also possible that the cumulative effect of certain cocktails of neuroactive peptides of placental origin could stimulate some brain receptors sufficiently to affect behaviour in pregnancy. Withdrawal of this stimulus post-partum could contribute to post-natal depression.

THE TACHYKININS

The tachykinins are an ancient family of neuropeptides containing the classical C-terminal pentapeptide Phe-X-Gly-Leu-Met-NH₂ motif. The first tachykinin to be characterised was substance P (Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂) – the most studied neuropeptide. Its gene, unusually, is not expressed in placental tissue.⁶

The other members of the tachykinin family are neurokinin A (formerly known as substance K), NKB and haemokinin (all 10-mers). The human homologue of haemokinin is endokinin, but it occurs as a 41-mer (Asp¹-Val-Lys³⁰-Thr³¹-Gly-Lys-Ala-Ser-Gln-Phe-Phe-Gly-Leu-Met-NH₂) as it lacks a double basic processing site at residues 30/31. A two-site immunometric assay detected significant concentrations of endokinin in human placental extracts.⁶ Thus, on C8 HPLC, placental endokinin elutes much later than NKB and, like the latter, is phosphocholinated.

Due to its size and phosphocholinated PTM, placental endokinin would be expected to have a long half life in the mother's blood. When NKB was considered to be the only tachykinin produced by the syncytiotrophoblast of the placenta, it appeared to be the local, albeit weak, agonist for the neurokinin 1 receptor (NK1R), mediating vasodilation in the placenta, improving local blood flow and diffusion transfer of vital substances.⁷ As synthetic endokinin(10-41) is as potent as substance P at the NK1R,⁶ it is more likely that the primary function of endokinin is as the principal placental NK1R agonist mediating local vasodilation – but could it have unwanted side effects?

NK1R AGONISTS, EMESIS AND SALIVATION

Vomiting or emesis has been recognised for centuries as a protective reflex after ingesting poisonous materials. The one condition in which

emesis has been the cause of much distress and confusion (particularly regarding what benefit it can impart) is pregnancy. In extreme cases (hyperemesis gravidarum), it can lead to the death of both mother and fetus.

Although the emetic action of substance P was reported 30 years ago,⁸ its complete absence from the placenta is probably why its direct role in pregnancy emesis has not been studied. I propose that the potent natural placental NK1R agonist, endokinin, should now be recognised as the likely cause of emesis in pregnant women. Endokinin may also cause the co-occurrence of excess salivation (sialorrhoea), as the sialogogic activity of substance P was reported many years ago⁹ as being mediated through the NK1R.¹⁰

NK1R ANTAGONISTS IN TREATMENT OF EMESIS

Selective non-peptide NK1R antagonists, most notably aprepitant, are widely used to control emesis after anaesthesia and chemotherapy.¹¹ Unfortunately, aprepitant interferes with the contraceptive pill and is not recommended for general use in pregnant women as it would cross into the fetus affecting its development.

In women previously diagnosed with diabetes insipidus, use of oral DDAVP (desmopressin) is safe during pregnancy. Enough survives digestion (due to its resistant D-amino acid content) to be efficacious, but it does not cross the placenta in appreciable amounts. Similarly, sendide (Tyr-DPhe-Phe-DHis-Leu-Met-NH₂), a NK1R antagonist, is also a protected peptide and reduces cisplatin-induced emesis in ferrets by targeting NK1Rs in the gut and the area postrema, the part of the medulla oblongata below the blood-brain barrier.¹²

As sendide would not be expected to cross into the fetus, could it become the drug of choice to treat morning sickness and sialorrhoea? In view of possible side effects in the fetus, it may not be advisable for 24-h dosage in extreme cases of hyperemesis gravidarum, but it may provide enough temporary relief for pregnant women to have nourishment by mouth, avoiding intravenous feeding and enabling arrest of the self-sustaining vomiting reflex. A sendide-containing mouthwash could however be a safe treatment for sialorrhoea.

PHIL LOWRY

Emeritus Professor, University of Reading

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IN PRAISE OF PIT STOPS

FROM OUR SCIENCE COMMITTEE CORRESPONDENT

Watching atypical telly at odd hours of the morning is one of the less well advertised side effects of having small children in the house. One Sunday morning, an insomniac nephew and I found ourselves watching the Grand Prix highlights, something I never do normally. After a deep silent study came the questions. 'Why does he keep stopping to take his wheels off? How can he win...? Other cars will beat him!'

My audience was unimpressed with my explanation of the need to have pit stops, that going round and round without stopping means that you might not even finish the race. To him the world was still one giant Scalextric figure of eight, and going as fast as possible for as long as possible was both fun and the only option.

Yet being locked in a groove can morph into being stuck in a rut. Projects can get stale and people can and do get tired. Not the kind of tired that an early night in your own bed can fix, more the creeping, insidious, gnawing tired that can go undetected by those afflicted and often requires a third party to point out and flag down.

The idea of needing to pause, change and do less to ultimately achieve more has been around for millennia. From the sabbatical year of ancient Hebrew law (the seventh year of a 7-year cycle in which the

land was left fallow) to the pop culture motif of change in the seventh year featured in Billy Wilder's film with Marilyn and the white dress, it seems whether you are a depleted Mediterranean vineyard or a stressed-out executive, 'year seven' is when change is required.

I suspect for the vast majority, what you do continues to be satisfying and rewarding, and that, for the most part, 'work is more fun than fun'. But what if things are not so good and an uneasy malaise has settled over an area that once occupied a special place in your heart?

Wiseacres can argue that it is wrong to use a precious resource to give people time for 'a bit of a think', on account of them being tired with all that sitting and thinking that they've been doing. However, my experience of people who have taken sabbatical leave is that they return to their institution and their day jobs energised and invigorated, with a sharper sense of purpose.

Mental pit stops still have a place in the modern age.

TONY COLL

Science Committee correspondent

IN SEARCH OF TEA, CRICKET, ENDOCRINE EXCELLENCE ... AND ELEPHANTS? A SRI LANKAN COLLABORATION

FROM OUR CLINICAL COMMITTEE CORRESPONDENTS

Last October, the Society was invited to join with the Endocrine Society of Sri Lanka to support their Annual Academic Sessions. As members of the Society for Endocrinology's Clinical Committee, we were fortunate to attend, and delivered symposia on pituitary disease, childhood endocrine conditions and hyponatraemia.

Endocrinology in Sri Lanka is relatively young, having only been recognised as a specialty for the last 16 years, through the hard work of the members of the Endocrine Society of Sri Lanka (ESSL; established in 1979; www.endocrinesociety.lk). Much of ESSL's success is attributed to Henry Rajaratnum, who we were lucky enough to meet. During Dr Rajaratnum's career, he has made the case for higher specialist training and its delivery through hub and spoke centres of excellence, as well as organising regular meetings and the publication of a journal.

The history of ESSL has seen strong links between endocrinologists in Sri Lanka and those in the UK, with Sri Lankan colleagues undertaking training opportunities at leading UK centres. The work of the ESSL continues at a pace.

The youthfulness of endocrinology in Sri Lanka was evident during the packed 3-day programme, which covered all aspects of diabetes, obesity and endocrinology, and was delivered by local, regional and international experts. All three of us were inspired by the strong national networks and international collaborations that the ESSL had formed.

We received an exceptionally warm welcome and the cultural reception, social programme and food were outstanding. We can vouch that the



Helena Gleeson, John Ayuk, Niki Karavitaki and Prasad Katulanda

ESSL is well on track to achieve its mission of 'achieving excellence in endocrinology'!

JOHN AYUK, HELENA GLEESON, NIKI KARAVITAKI AND PRASAD KATULANDA

John, Helena and Niki are all members of our Clinical Committee. Prasad Katulanda is President of the Endocrine Society of Sri Lanka. For more information on the ESSL, visit www.endocrinesociety.lk.

WELCOME TO YOUR NEW OFFICERS!



Our new Officers Elect started shadowing the Society's current Officers in November 2014, and will take up their posts at the 2015 AGM during the Society for Endocrinology BES conference in Edinburgh.

We are sure you will join us in welcoming Karen Chapman (Edinburgh), Barbara McGowan (London) and Simon Pearce (Newcastle upon Tyne) to their new roles. We at *The Endocrinologist* thought you would like to get to know them better, and find out why they chose to work with the Society, and what they are looking forward to in their new roles.

KAREN CHAPMAN GENERAL SECRETARY ELECT



'I became hooked on endocrinology through listening to a seminar by Keith Yamamoto on the glucocorticoid receptor (GR). At the time (1985) I was a postdoc working on a microbial ligand-activated transcription factor (a model for the GR then). I moved to Edinburgh later that year to work on a steroid-related project and have worked here on steroids and their receptors ever since.

My association with the Society for Endocrinology started through my membership of the Biochemical Society. I served on the Hormone Group Committee, then a joint committee between the two societies. My subsequent close association with the Society for Endocrinology has included chairing the Science Committee, and serving on the Programme Committee, the Publications Committee (and a journals review working group) and Council.

It is a huge honour to be elected as the next General Secretary. Reflecting on my predecessors, I have a lot to live up to! What do I see as the big challenges? In a competitive and time-scarce world, it is vitally important to keep the Society relevant to its members, ensuring we cater for both our clinician and our basic science membership. We need to attract and retain our younger members especially, supporting training, education and career development.

The Society benefits enormously from Bioscientifica, our commercial subsidiary and main publisher of Society journals. Bioscientifica provides the financial support that underpins many Society grants and activities. It will be crucial to ensure it maintains its healthy position. Challenging but exciting times ahead!

BARBARA McGOWAN TREASURER ELECT



'It is with some excitement and trepidation that I take over the role of Treasurer. I have been granted this honour on the basis of my previous life as an investment banker, prior to my medical career.

I started off by studying biochemistry at Hertford College Oxford, but moved to 'the City' as a pharmaceutical equity analyst for Barclays, and subsequently to JP Morgan to market foreign exchange options. The banking experience allowed me to sample the exciting world of corporate finance, hectic trading floors and pressurised dealing rooms.

Five years later, I saw the light, and realised that there was life after money. I headed back to medical school and then never left the dizzy heights of the NHS. Most of my medical life has been spent training in London, never far away from science and academia, including a PhD at Imperial in Steve Bloom's lab, and over 5 years in my new home at Guys & St Thomas' Hospital.

Recently, I have been involved in the Society's finances as a member of the Finance Committee. I especially enjoy overseeing the management of the Society's investment portfolio, and giving the investment managers a run for their money!

Graham Williams has done a great job over the last 5 years, steering the Society through one of our biggest recessions and turbulent times of economic uncertainty. I hope I can live up to this challenge and ensure the Society enjoys a healthy balance sheet and remains financially viable for years to come. If there are any budding endocrinologists with financial experience amongst you please come and find me!

SIMON PEARCE PROGRAMME SECRETARY ELECT



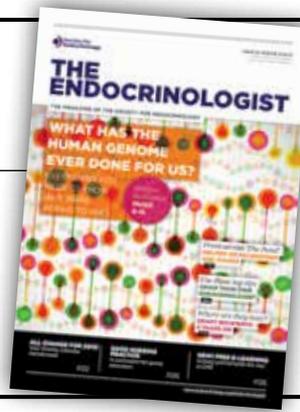
'I'm based in Newcastle upon Tyne, where my time is split between NHS clinical endocrinology and university-based research.

I trained in Hammersmith, Boston and Newcastle. Although my research career began studying the calcium-sensing receptor, I am now working on endocrine auto-immunity, particularly Graves' and Addison's diseases.

My first Society for Endocrinology BES conference was in Bournemouth in 1994, and I have attended every one since. I still relish the excitement of listening to a presenter who is asking or answering the same questions that have been bothering me. The SfE BES programme has always had a high standard, and I hope that over the next few years we can enthrall the UK endocrine research community with high quality science, whilst continuing to provide pertinent and varied CPD for clinical endocrinologists.

The conference must reflect the diverse interests of the Society's membership and I would be very pleased to hear your suggestions for the programme. Please just drop me an email at the address below.'

If you would like to contact any of our Officers Elect, please email members@endocrinology.org.



YOUR VIEWS ON THE ENDOCRINOLOGIST

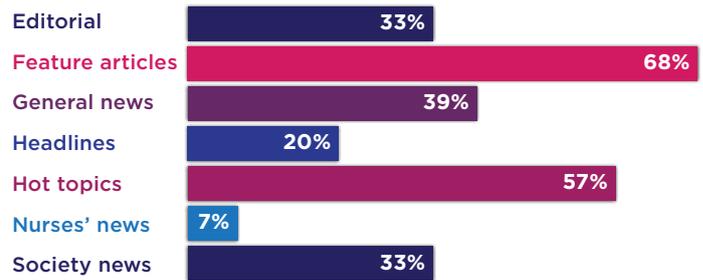
In summer 2014, we asked you, the readers of *The Endocrinologist*, to let us know your thoughts about the magazine: what you like and don't like and what we could do better. We received 54 responses, and below is what you told us.

The Editorial Board is reviewing the feedback and looking at how we can improve your enjoyment of *The Endocrinologist* and its value to you. Details will follow soon!

We are always keen to hear what you think about *The Endocrinologist*. So, if you didn't fill out the questionnaire, you can still contact us at endocrinologist@endocrinology.org.

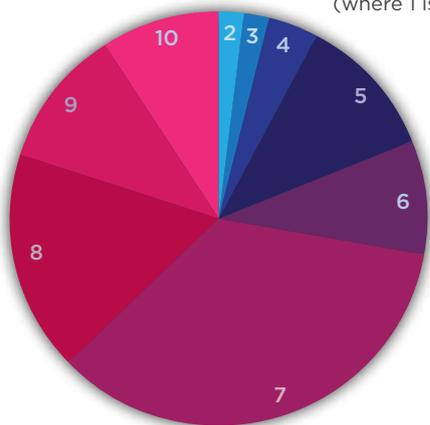
JENNIE EVANS
Managing Editor, *The Endocrinologist*

WHAT ARE YOUR TOP THREE FAVOURITE SECTIONS OF THE ENDOCRINOLOGIST?

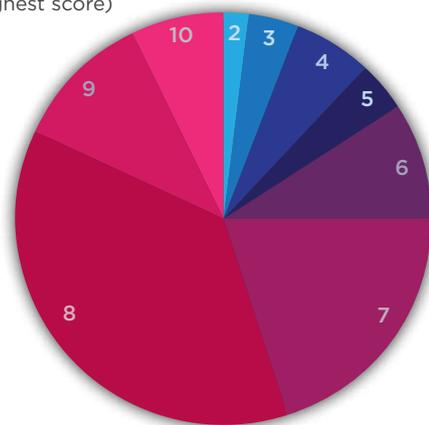


HOW DO YOU RATE THE DESIGN OF THE ENDOCRINOLOGIST?

(where 1 is the lowest and 10 is the highest score)



HOW DO YOU RATE THE OVERALL CONTENT OF THE ENDOCRINOLOGIST?



NEW! EQUIPMENT GRANT - UP TO £10,000

2015 sees the launch of a brand new grant from the Society. The Equipment Grant, worth up to £10,000, is an exciting opportunity for members undertaking research as principal investigators, and is aimed at those in a first lectureship or holding a charity fellowship. This is valuable support if you want to establish a laboratory and purchase vital equipment.

You can submit applications to fund pieces of equipment, part pieces of larger equipment or basic lab items. Requests to fund maintenance will also be considered if justified appropriately.

Up to three Equipment Grants will be offered per annum, and members can receive the grant once. Application deadlines are on 27 May and 27 November each year, starting on 27 May 2015.

Learn more about this fantastic new funding opportunity at www.endocrinology.org/grants/grant_equipment.html.

HAVE YOU RENEWED?

Do you want uninterrupted access to the full range of Society benefits, including funding, events, support and development opportunities? If so, don't forget to renew your membership for 2015! Visit www.endocrinology.org/membership for more information.

APPLY FOR YOUR EARLY CAREER GRANT TODAY!

Are you an early career endocrinologist looking for funding assistance to help you 'climb the ladder'?

Worth up to £10,000 each, our Early Career Grants support endocrinologists up to 10 years post-PhD.

The application deadline is 27 May 2015. See www.endocrinology.org/grants/grant_earlycareer.html.

EARLY CAREER ENDOCRINOLOGISTS: HAVE YOUR WORK SEEN AND HEARD!

Are you the next Early Career Prize Lecturer? Two winning abstracts will be selected for presentation in a prize session at the 2015 Society for Endocrinology BES conference, for which an honorarium of £750 is payable. The deadline for submissions is 10 April 2015. You can find out more at www.endocrinology.org/grants.

LET'S TALK ABOUT HORMONES!

WRITTEN BY SAFFRON WHITEHEAD



The most recent survey of public attitudes to science¹ revealed that 72% of adults in the UK say it's important to know about science in their daily lives, and 91% of 16-24-year-olds agree that young peoples' interest in science is important for our future prosperity. Yet only 22% believe scientists are good at communicating.

As a charitable organisation, an important part of our Society's remit is to excite the public's interest in endocrinology and its impact. Hormones are intrinsically fascinating and affect many areas of public health. This gives us the exciting

opportunity to tell powerful and meaningful stories that enhance understanding and engagement with our discipline.

The Society's Public Engagement Committee has a new plan for 2015 onwards that focuses on a range of target audiences, including under-18s, family groups and patients. The plan identifies the best ways of reaching these people and making a big impact, as well as the key partners with which we should collaborate.

A large part of this activity will involve developing our public-facing website *You & Your Hormones* (www.yourhormones.info) to meet the

needs of our target audiences. We need help from you, the members of the Society, to add or review the current website content. Your help is also sought in expanding our activities to include educational resources, patient support groups and family groups, and in suggesting hands-on activities for school children and science festivals.

It is only with your input and help that we can undertake more public engagement and outward-facing work. Please get involved – I look forward to hearing from you with offers of ideas or support!

SAFFRON WHITEHEAD
Chair, Public Engagement
Committee



REFERENCE

1. Ipsos MORI 2014 *Public Attitudes to Science* <http://bit.ly/1HA0tHe>

You can volunteer to help our Society with public engagement activities by emailing saffron@sgul.ac.uk

EDINBURGH 2015: BE PART OF IT!

SOCIETY FOR ENDOCRINOLOGY BES CONFERENCE 2-4 NOVEMBER 2015

BRINGING YOU THE BEST IN THE FIELD

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- Distinguished faculty of international experts
- Diverse programme spanning basic science, translational research, clinical investigation and clinical practice
- Excellent learning and networking opportunities for all!

PROGRAMME PREVIEW

- **Symposia** featuring endocrine tumours, biological therapies, corticosteroids and model systems
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- **Clinical Management Workshops** covering topics from hirsutism and gynaecomastia to steroid abuse and chronic fatigue
- **Full programme coming soon!**

DEADLINES FOR YOUR DIARY

- Abstract submission 15 June
- Registration Grant applications 4 May–6 July
- Conference Grant applications 15 July
- Early bird registration 21 September
- Find out more at:
www.endocrinology.org/meetings/sfebes

MAKE YOUR WORK PART OF SFE BES 2015

Share your research with an international forum of clinicians and researchers. Find out how to submit your abstract at www.endocrinology.org/meetings/sfebes.

SFE BES CONFERENCE AND REGISTRATION GRANTS

Society grants will help you attend SFE BES 2015. See www.endocrinology.org/grants for details and online applications:

- **Conference Grants** for members
- **Registration Grants** (previously known as 'Free Places') for undifferentiated trainees and students

DON'T FORGET, ONLY ABSTRACT AUTHORS CAN:

- Apply for a Conference Grant
- Receive any of the 20 awards and prizes awarded at SFE BES 2015.



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BECOMING THE LEADING PUBLISHER IN ENDOCRINOLOGY AND BEYOND



WRITTEN BY KATHRYN SPILLER

Our Society is supported by the profits of its commercial subsidiary, Bioscientifica. Bioscientifica collaborates with learned societies worldwide to provide bespoke, world-class publishing and association management to the biomedical community. Owned by the Society for Endocrinology, Bioscientifica publishes five of the Society's six official journals, within its current portfolio, which includes high impact subscription titles, open access journals and online resources.

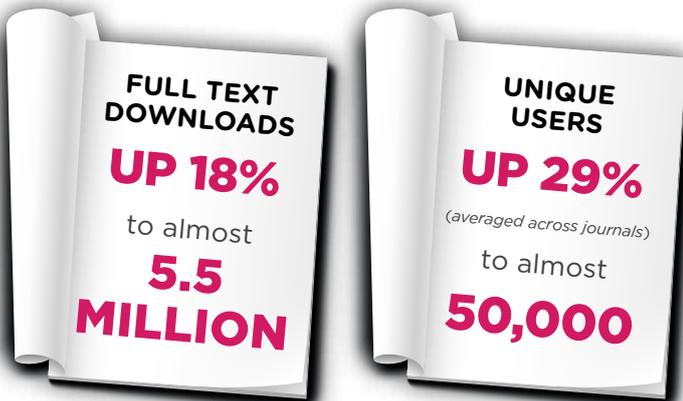
journal, internationalised editorial boards, launched new products and reduced costs, while at the same time achieving an increase in quality across the board.

This has meant we are able to sustain our growth and ensure that Bioscientifica can continue to support the work of the Society for Endocrinology.

KATHRYN SPILLER
Head of Publishing, Bioscientifica

A PUBLISHING SUCCESS STORY IN THREE SHORT YEARS, 2012-2014

INCREASED JOURNAL READERSHIP



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BIGGER GLOBAL PROFILE



29%
increase in submissions to more than
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<p>MARCH 2012: <i>Endocrine Connections</i></p>	<p>MARCH 2013: <i>Endocrinology, Diabetes & Metabolism Case Reports</i></p>	<p>MAY 2013: <i>Bone Abstracts</i></p>	<p>MARCH 2014: <i>Bioscientifica Abstracts</i></p>	<p>MARCH 2014: <i>Echo Research and Practice</i></p>	<p>SEPTEMBER 2014: <i>Reproduction Abstracts</i></p>
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THE NEW REGISTRAR'S SURVIVAL GUIDE

WRITTEN BY SAM O'TOOLE

Clutching your brand new national training number, you enter your new ward, your new kingdom. This is the first day of the rest of your life. So, now what?

Your first day as a registrar probably comes with mixed emotions. Some will be positive, in recognition of the achievement it represents, and perhaps the misguided assumption that the days of writing TIA ('to take away') prescriptions for hospital discharge are behind you. Others will be less so.

We are naturally nervous about the unknown and the path untrodden. It can feel lonely at first. These are your first few steps out of the warmth of the senior house officer-dominated mess, where you no longer feel you belong. On the horizon is the goal – a certificate of completion of training (CCT) and the independent practice it promises. But how best to make the journey?

The recent and extensive codification of medical postgraduate education means everything must be proven, evidenced, documented and reflected upon. No longer is it acceptable just to turn up and be a good doctor – you have to show that you are one. Indeed, it can sometimes appear that to be simply 'average' or competent is to fail. We must all excel – quite how this fits into our own Gaussian distribution is never explained.

With this in mind, here are some thoughts about themes that may, or may not, play on your mind as you enter your ST3 year.

ePORTFOLIO

Having successfully navigated core medical training, the ePortfolio will be all too familiar. Love it or loathe it, it is here to stay, scrutinising your progress and identifying areas for improvement. Embrace it early (and whilst there is still time), keep it updated with developments in your life and it will see you through to the end. It may be time-consuming and feel like a chore, but it's better to have it on your side.

Keep an eye on the summary page of the curriculum (available on the Joint Royal Colleges of Physicians Training Board (JRCPTB) website; www.jrcptb.org.uk) for a digestible account of what is required at your Annual Review of Competence Progression (ARCP) on a year-by-year basis.

'No longer is it acceptable just to turn up and be a good doctor – you have to show that you are one. We must all excel – quite how this fits into our own Gaussian distribution is never explained.'

GENERAL INTERNAL MEDICINE

Whatever your thoughts about it, general internal medicine (GIM) is the cornerstone of inpatient practice. Sticking your head in the sand might be initially comforting, but you will not be able to escape it. Remember that you are as much a trainee in GIM as in diabetes and endocrinology – you will almost certainly undertake a CCT in both – and so give it the time, respect and share of your study budget that it deserves. Check with colleagues early, as some deaneries require separate GIM supervisors' reports and even a dedicated GIM ARCP.



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DIABETES AND ENDOCRINOLOGY

Giving specialty advice will probably be new territory. You can't and won't know it all, on either your first or your last day as a registrar, but certain topics are predictable. Depending on your local diabetes set up, you may or may not have a host of inpatient insulin titration to keep you busy. Electrolyte imbalance is likely to predominate in endocrine consultations, whilst GP calls will often concern wonky thyroid function tests or other incidental discoveries.

Again, try and read the curriculum early and identify when and where you can fulfil your training needs. Planning ahead is important, as many of the more esoteric clinics will happen infrequently, and there can often be 'competition' to attend. A word of warning here: 'winning' a clinic attendance may provide a curriculum link but can cause discontent amongst your cadre. You may want to swap a shift, or apply for a job, with these people in the future – so think carefully and don't burn your bridges.

OUT OF PROGRAMME

Whether you want experience, research or training, there are a wealth of opportunities available to tailor your own bespoke training programme. Although there is no hurry to sign up, it's worth giving it some thought sooner rather than later, as application deadlines can be easily overlooked and prospective approval is needed before the JRCPTB will count it as part of your training. Don't underestimate how long it can take to find a research placement, particularly if you need to secure funding too. Finally, don't forget that you are not tied to your home deanery – the world, as they say, is your oyster.

Most importantly, make friends with those on your rotation. You will quickly realise that you are not alone and those first steps have been taken many times before.

SAM O'TOOLE
Honorary Specialist Registrar in
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London

WHAT'S IN IT FOR YOU? JOINING A REGIONAL ENDOCRINE NETWORK AS A TRAINEE

WRITTEN BY ANNA MITCHELL



The Northern Endocrine Network was set up in 2013 to bring together members of each of the endocrinology units of the Northern Deanery (now known as Health Education North East) for a quarterly meeting. Health Education North East provides postgraduate medical training across North East England and northern Cumbria.



Members of the Northern Endocrine Network

The purpose of the Northern Endocrine Network is to develop links between units and establish regional guidance and pathways for endocrine conditions, with the ultimate aim of facilitating the provision of high quality, uniform patient care across the region and promoting regional collaboration in quality improvement, research and audit projects.

WHAT IT'S MEANT TO ME

I was invited to join the Network in 2013 as a trainee representative. I was initially sceptical about the benefits that I might gain personally from joining a regional network. However to develop those elusive leadership and management competencies, and to tick a few ePortfolio boxes, I accepted the invitation. Since joining, I have been surprised at how much I have gained, as a young endocrinologist, from participating in the Network's meetings and projects.

As a specialty trainee in diabetes and endocrinology, I rotate to different hospital trusts annually. This has some definite advantages: it means that I can see how different units work, pick up tips from consultants across the region and gain unique clinical experience in centres of excellence. As a bonus, I've picked up some local dialect along the way and sampled some regional delicacies – including the famous 'Middlesbrough parmo'.

The disadvantage of a rotation is that, just as you begin to feel part of the team, have familiarised yourself with the local protocols and are beginning to feel comfortable at work, you have to move on and begin again.

The Network has provided me with a great opportunity to meet endocrinology specialists from across the North East, as an equal, in an informal setting. This means that when I rotate around the region, at least I now see more friendly faces and get less of the 'new girl at school' anxiety in my first days. In addition, as we are developing regional protocols and promoting the use of national and international guidelines across the region, rotating on an annual basis is less painful because practice is becoming a little more uniform between trusts.

ADDED ADVANTAGES

The Network has also allowed me to get involved in a regional quality improvement project, developing a pathway for access to specialist genetic testing for monogenic endocrine conditions to be used across the North East. This project's main aim is to ensure equity of access to specialist services across the region for patients with these relatively rare conditions.

It has been great to complete a meaningful project focused on quality improvement that

will ultimately improve patient care. In the process, I have developed transferable and valuable skills in leadership, negotiation and project management.

The Network is planning other regional projects and, increasingly, trainees are getting involved and taking the lead. This gives trainees a unique presence in endocrinology in the North East, and a powerful voice in setting priorities in the regional agenda. We are currently developing a Network website where local, national and international guidelines and regional endocrinology news will be posted. We hope this will be used widely by endocrinologists in our region.

FULFILLING YOUR WISH LIST

So, what do clinical trainees want these days? The wish list is short and relatively simple: excellent clinical training, to feel like a valued and valuable member of the multidisciplinary team, to get through the Annual Review of Competence Progression (ARCP) without the need for counselling and to come out 'at the other end' with their dream job.

What does joining a local endocrine specialist interest group or network offer to trainees? Joining the Northern Endocrine Network has helped me to develop some new skills, allowed me to contribute to improving clinical care in the region, given me a voice in regional specialty matters and helped me to integrate into endocrinology in the North East by getting to know consultant colleagues on an equal footing.

In terms of the dreaded ARCP, I can't pretend that membership of the Network is a golden ticket to a positive, pain-free outcome, but it certainly helps me to provide supporting evidence for some of the essential generic curriculum competencies. It also complements my clinical portfolio, which I hope in time will help me to land my dream job.

I would encourage other young endocrinologists to join their local network. And if there isn't one? Set one up!

ANNA MITCHELL

Academic Clinical Lecturer and trainee in Diabetes and Endocrinology, Northern Deanery

For more information on the Northern Endocrine Network, visit their website (currently in development) at <http://nen.dcwd.co.uk>.

ENDOCRINE NURSE UPDATE: WHAT COULD IT MEAN FOR YOU?

WRITTEN BY CYNTHIA G MAGTOTO



In July 2014, I was successfully appointed as Deputy Endocrine Nurse Specialist. I previously covered maternity leave for our endocrine specialist nurses, and having a permanent post in endocrinology is an exciting opportunity.

My colleague encouraged me to attend the Endocrine Nurse Update in Birmingham last September, to help me with my new post. Applying for the conference was straightforward. Browsing the programme was both exciting and overwhelming. While there were some topics which were familiar to me, like growth hormone deficiency and testosterone replacement, there were also some that were unfamiliar, such as parathyroid disorders and late effects.

I felt anxious when I arrived at the conference as I did not know anybody, except for my colleague who is a member of the Committee. She introduced me to the attendees, who were very welcoming, and I immediately started to feel at ease.

As I expected, the lectures were delivered well, by experienced endocrine specialist nurses and consultants. I gained more knowledge of the topics that were familiar, and improved my understanding of those that were new to me. As well as the lectures, there were networking speed sessions and parallel workshops. I enjoyed these as we were able to discuss, explore, debate and learn what other nurses do in their practice.

In between lectures we had breaks, which gave me an opportunity to mingle with other nurses. The 'new' endocrine nurses' enthusiasm to learn was encouraging, and the endocrine specialist nurses who have been in the field for a considerable time have dedication and expertise that are inspiring. I also met different patient groups; these give vital information, enabling me to better support my endocrine patients and other healthcare professionals.

The 2-day Endocrine Nurse Update swiftly came to an end. The conference gave me not only the opportunity to learn, but also opened doors for communication with other endocrine nurses. Now, if I have any queries, I can just click a button and send an email to the wider community of endocrine specialist nurses in the UK, who are so willing to help.

'Now, if I have any queries, I can just email the wider community of endocrine specialist nurses, who are so willing to help.'

I am glad I attended the Endocrine Nurse Update, and would highly recommend the next conference, which takes place in Birmingham on 16-17 March 2015.

CYNTHIA G MAGTOTO
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**ENDOCRINE NURSE
UPDATE 2015**
16-17 March 2015, Birmingham, UK

www.endocrinology.org

**New format
for 2015**

 Society for
Endocrinology

LISA SHEPHERD

NURSE COMMITTEE CHAIR



This year sees publication of the second edition of the *Competency Framework for Adult Endocrine Nursing* (see advert on page 16). For many years, endocrine nurses requested the development of UK-wide standards for adult endocrine specialist nursing. The first edition was launched in 2013, and built on the work already undertaken by our paediatric endocrine nurse colleagues.

When endocrine nurses collaborate and utilise their knowledge and experience to develop such a framework, it highlights what can be achieved in order to enhance the care of adults with endocrine disorders. Not only has this proved immensely valuable in the UK, it has also been acclaimed worldwide by our fellow endocrine nurse colleagues, thus forming valuable links.

Following feedback from endocrine nurses nationally, the new edition now includes competency guidance on benign adrenal tumours, hypo- and hyperparathyroidism, osteoporosis, and polycystic ovary syndrome. The framework focuses on skills, interventions and specialist knowledge that are specific to nurses working as adult endocrine nurses.

This vital understanding can be gained by attendance at conferences and nurse meetings. Attendance not only improves knowledge but also establishes important local and national links through networking and forming professional relationships. This is eloquently explained by Cynthia Magtoto, in her article on the preceding page about her first experience of Endocrine Nurse Update, in September 2014.

Conference grants are available from the Society for Endocrinology to attend Endocrine Nurse Update 2015 in Birmingham on 16–17 March; the deadline for applications is 15 March 2015. I look forward to seeing you there.

With such an exciting start to 2015, who knows what else endocrine nurses will achieve in the year ahead...

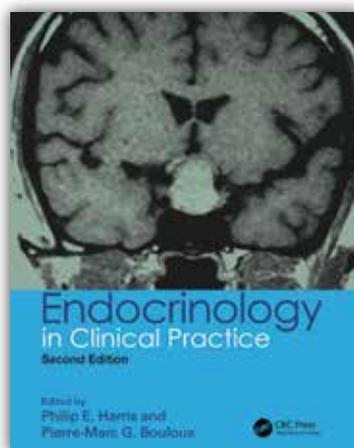
LISA SHEPHERD

ENDOCRINOLOGY IN CLINICAL PRACTICE

Eds PE Harris & PMG Bouloux, CRC Press, 2014, 2nd edn, 603pp, Hbk, £121.00, ISBN 978-1-841849515

Endocrinology is a complex subject in which basic science drives forward new clinical and therapeutic manoeuvres on a regular basis. Keeping up to date and making sure that our practice is solid and evidence-based can be challenging.

The new second edition of this textbook is a welcome, authoritative guide to the whole of endocrinology, and is suitably different in style and approach from that other excellent recent key text *Clinical Endocrinology* by Saffron Whitehead and John Miell.



As well as the expected updates to the existing chapters (with topics ranging from adrenal disease to endocrine emergencies), a great deal of new research data has also been incorporated, along with information about the latest diagnostic and imaging techniques. We also get to find out about the safety concerns related to existing therapies, for example the risks of valvulopathy

with low dose dopamine agonists, and the safety of testosterone replacement therapy in the ageing male.

I particularly liked the chapter on endocrine problems in pregnancy. There are potential consequences for both mother and baby if these are not treated properly. Fortunately I haven't had a case of pheochromocytoma misdiagnosed as pre-eclampsia yet. The chapter by David Clemmons on insulin-like growth factor-1 as a metabolic hormone is both very readable and comprehensive, and its role and behaviour in various different disease states from diabetes to osteoporosis are well described.

Other highlights of the new edition include a whole appendix on pituitary function testing by William Drake and Peter Trainer, which is a good overview, especially for trainees. There is a great deal of content (noting the editors and authors) on neuroendocrine tumours and their diagnosis and management. Coverage includes changes in the best types of diagnostic imaging for endocrine disease and the increasing use of PET scanning. In addition, you will find the latest information on research into the characteristics of familial isolated pituitary adenomas which, as anybody who has heard Márta Korbonits talk on the subject will know, makes a good read.

Overall, this is an excellent book with up to date content for the practising endocrinologist. Every department would certainly benefit from having a copy to hand.

PAUL GRANT
Consultant Endocrinologist,
Royal Sussex County Hospital, Brighton

GENERAL NEWS

ACROMEGALY GUIDELINES

The Endocrine Society has issued new clinical practice guidelines on the evaluation and management of acromegaly, published in *Journal of Clinical Endocrinology & Metabolism* 2014 **99** 3933–3951.

A copy of the guidelines can be found at <http://dx.doi.org/10.1210/jc.2014-2700>. The guidelines were co-sponsored by the European Society of Endocrinology.

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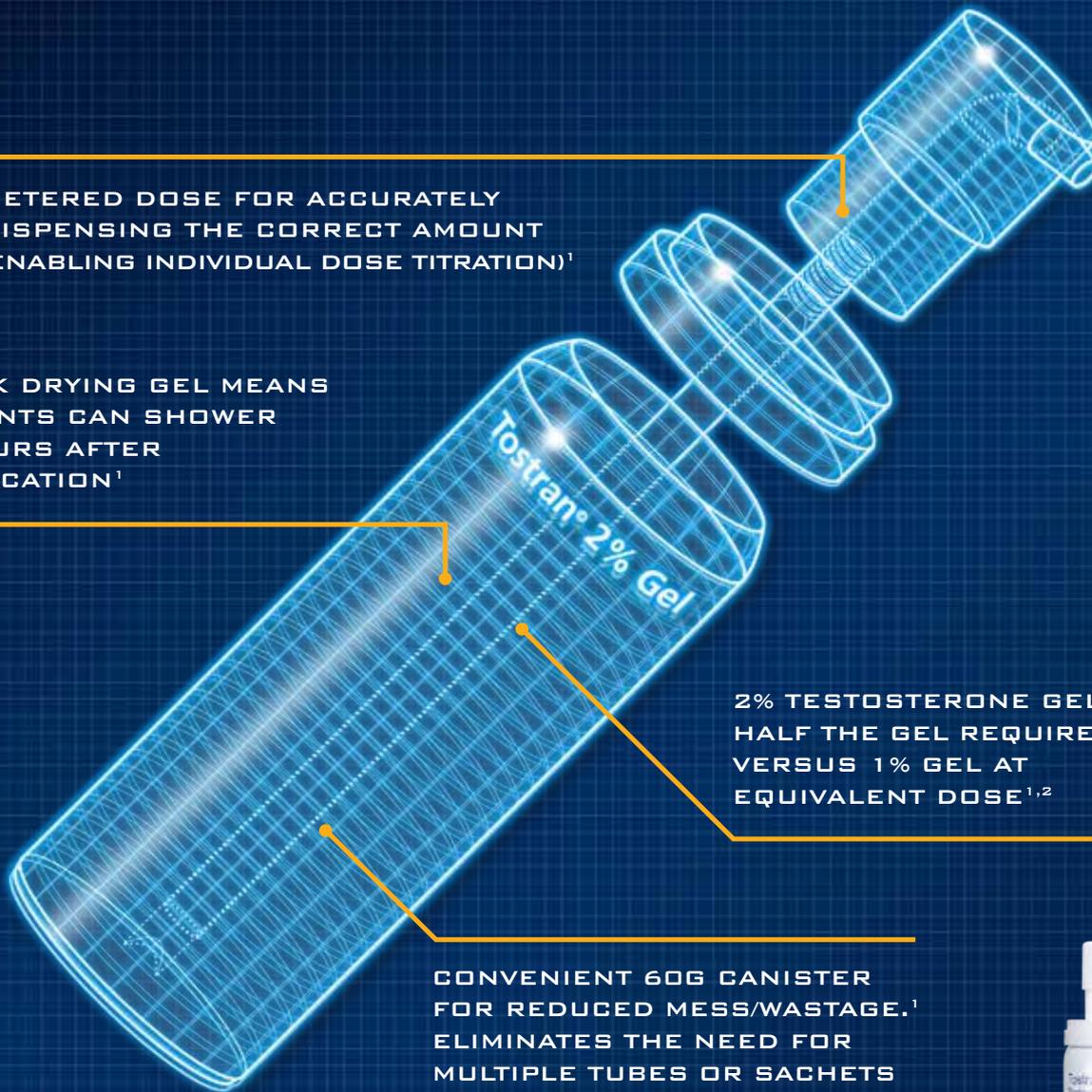
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References: 1. Tostran[®] Summary of Product Characteristics, June 2010. 2. Testogel[®] Summary of Product Characteristics, November 2006. **Date of preparation:** February 2014. **Job code:** M015/1224