



ESE News

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THE EUROPEAN HORMONE SOCIETY

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Endocrinology and our environment

Including:

The impact of
endocrine disruption

What links cancer
to diet

Acromegaly in
industrial Sicily





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www.ese-hormones.org

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Editorial

Welcome to this issue of *ESE News*. I am delighted to be writing my first Editorial to you as ESE President.

As we are all very aware, our environment has an impact on our own endocrinology and that of our fellow creatures. In this issue, we take a broad look at the impact of endocrine disruptors, as Evanthia Diamanti-Kandarakis considers the financial implications of these pervasive pollutants (page 7). On page 10, Wouter de Herder examines their history, as the impact of contamination with non-endogenous endocrinologically active compounds has gradually become apparent to humans around the globe.

Of course, our diet constitutes an important part of our environment: 'We are what we eat!' I had the privilege of interviewing Lewis Cantley at ECE 2015, and his studies on the impact of diet and obesity on metabolism and oncology offer a profound insight into the mechanisms by which a typical 'Western diet' could drive tumorigenesis. Read page 9 to fully appreciate the perils of weight gain and the importance to your health of a diet low in rapid release carbohydrates.

Salvo Cannavò, an endocrinologist on Sicily, recounts his experiences of

environmental endocrinology in 'A day in the life...' on page 11. With his team, he has studied the epidemiology of acromegaly in the industrial areas of this otherwise beautiful island. It is noteworthy that Salvo, his fellow southern Italians and their healthcare system are also addressing the significant environmental challenges posed by caring for many migrants, with a spirit of great generosity.

Elsewhere you will find much news from the world of endocrinology. We reflect upon the sad and untimely loss of our friend and colleague Bruno Allolio (page 4). We also look forward keenly to new opportunities, such as the forthcoming European Congress of Endocrinology in Munich on 28–31 May 2016 (see page 3).

I wish you every success in your current endeavours, whatever your areas of interest. If you would like to contact me with suggestions or feedback about your Society, please email ese.president@endocrinology.org.

AJ van der Lely
ESE President
Co-Editor of *ESE News*

From the ESE office

It is, of course, essential that ESE has a clear direction and overall strategy. ESE's current vision (see www.ese-hormones.org/about) formed the basis of our strategic plan for 2011–2016.

The vision anticipated that 'By the end of the period, ESE will have a distinctive European flavour, creating an inclusive community that takes advantage of the diversity found within Europe. It will be an innovative society that responds rapidly to the changing needs of clinicians and researchers. It will also provide authoritative and independent information to the public.'

With AJ van der Lely now in place as President, we are thoroughly reviewing the document to ensure it is still appropriate for the future, taking into account all we have learnt and experienced. When the

vision was set, just 5 years after ESE's launch as a membership society, the Society was very young.

Our achievements in less than 10 years seem incredible: an ever-improving congress, an increasing raft of educational activities, our own guidelines, the growing impact of our fully owned journal *European Journal of Endocrinology*, and an expanding range of grants and awards.

We will tell you more as the review develops, and you will also be consulted. We take nothing for granted and depend on all of you to tell us your thoughts, both positive and constructively critical, to help us improve European endocrinology.

As ever, please get in touch at any time on info@euro-endo.org.

Helen Gregson
ESE General Manager

Abstract deadline:

1 February 2016

Early bird registration:

28 March 2016

Register today!

www.ece2016.org

Cushing's syndrome: a seminal meeting

The October issue of *European Journal of Endocrinology* contains 13 topical reviews on Cushing's syndrome, co-ordinated by Martin Reincke (Munich).

These dedicated reviews summarise the main presentations at the 1st IMPROCUSH (Improving Outcome in Cushing's Syndrome) Symposium in October 2014, which attracted over 100 world-leading experts. It supported discussion of challenges and unsolved issues, triggering novel collaborative projects to develop more effective approaches to treatment.

This collection of reviews is free to read at www.eje-online.org/content/173/4.toc.

New Editor-in-Chief for ESE journals

Dr Sofianos Andrikopoulos is the new Editor-in-Chief of *Journal of Endocrinology* and *Journal of Molecular Endocrinology*, two of ESE's official journals (governed by a joint Editorial Board).

Dr Andrikopoulos is a National Health and Medical Research Council of Australia Senior Research Fellow, Head of the Islet Biology Research Group at the University of Melbourne and President of the Australian Diabetes Society.

With this experience, he is well positioned to build on the journals' successful development under Professor Adrian Clark, whom we thank for his excellent leadership.



Make way for Munich!

18th European Congress of Endocrinology
Munich, Germany, 28–31 May 2016

ECE 2016 will welcome delegates from all areas of endocrinology, and all parts of the globe! The Congress programme will certainly satisfy your interests, whether you are a scientist, clinician, nurse or trainee.

The ICM (Internationales Congress Center München) will be our venue. One of the world's most modern convention centres, it lies in the landscaped exhibition grounds of the Messe München.

Here, you will enjoy a wide selection of prize and plenary lectures, symposia, debates and Meet the Expert sessions. Clinical management workshops will cover state-of-the-art therapy and diagnosis of endocrine disease, while

new scientific approaches sessions will cater for basic scientists and interested clinicians. Special sessions will serve young endocrine scientists and endocrine nurses, with plenty of networking opportunities.

You can find more, including the programme, at www.ece2016.org. We look forward to welcoming you to Munich!

Ilpo Huhtaniemi (UK/Finland)
Chair, Programme Organising Committee (POC)

Robin Peeters (The Netherlands)
Ewa Rajpert-de Meyts (Denmark)
Joint Co-Chairs, POC

Günter Stalla (Germany)
Chair, Local Organising Committee

ESE BASIC ENDOCRINOLOGY COURSE: ENDOCRINE AND NEUROENDOCRINE CANCER

Porto, Portugal,
17–19 February 2016

Registration opens soon for this exciting course on the theme 'Endocrine and neuroendocrine cancer: beyond structural genetic alterations of oncogenes and tumour suppressor genes'

Featured topics:

- Metabolism rewiring
- Stem cells and stemness markers in carcinogenesis
- Exosomes and miRNA
- Mechanisms of immortalisation and survival
- Animal models in the study of carcinogenesis
- Genetics and epigenetics
- Proliferation and apoptosis as therapeutic targets in tumours

Find out more at:

www.esbasicsciencecourseporto2016.admeus.net



Diabetes, Obesity and Metabolic Syndrome

Nafplion, Greece,
17–19 April 2015



Young Greek scientists (17 medical undergraduates and 18 residents in endocrinology and postgraduates) attended this seminar 'Diabetes, obesity and metabolic syndrome: from basic research to clinical practice'.

It was organised by Christos Mantzoros, Professor of Endocrinology, Diabetes and Metabolism at Harvard Medical School (Boston, MA, USA; pictured) in collaboration with the Academy of Athens, Greece. Teaching was by faculty from Harvard and Greece.

Provision of an introduction to research methodology meant attendees not only received the latest clinical information about obesity and metabolism, but also an understanding of how to transition from clinical practice questions at the bedside to the translational research methodology that could provide answers. They then also learnt how apply this knowledge back in the clinic.

All attendees were keen to use what they learnt when they returned to their institutions, with the ultimate goal of benefiting patients. The participants are extremely grateful to Professor Mantzoros and his team for making this possible.

Bruno Allolio

Bruno Allolio sadly passed away in August 2015. Bruno was an innovative endocrinologist, an empathetic doctor, an inspiring teacher and a dedicated mentor. A true European, he had a wide network of friendships and collaborations. Amongst his many ties, he was a long-standing Editor of *European Journal of Endocrinology* and a strong voice for ESE, serving on its first Executive Committee, and being made an honorary member in 2014.

Bruno was excited by the intellectual challenge of endocrinology. He trained at the University Hospital of Cologne, later spending two postdoctoral periods abroad, at St Bartholomew's Hospital in London and at the National Institutes of Health in Bethesda, MD, USA. In 1992, he took the Chair in Endocrinology at the University of Würzburg and created a highly active research group, covering a breathtaking range of subjects, focusing around the adrenal.

Bruno was a fantastic mentor, and many of his trainees became close friends. He encouraged us to strive to inspire the next generation of endocrinologists. Bruno had a great sense of humour and never took himself too seriously.

His perspective on life was profoundly challenged after being diagnosed with a chronic life-threatening illness in 1998. However, he never took his mind off the scientific 'ball'. He told us that facing a life-threatening illness



also had benefits, such as increasing his focus even more consciously on his children as they grew up.

As a strong believer in medical progress through research, he fought his illness with the latest advances, and appeared to succeed. However, in 2013, he endured months of intensive care after contracting swine flu. Following an amazing recovery, he was again struck by illness, and underwent surgery and radiotherapy over the last 12 months. In the end, death was kind and greeted with relief. Our thoughts are with his wife Margarete and their three children, Christoph, Philip and Friederike.

'Ideas are cheap' was one of his sayings, but we should add 'Ideas are cheap for a great mind' – we will sorely miss Bruno Allolio and his ideas.

Wiebke Arlt (Birmingham),
Felix Beuschlein (Munich),
Martin Fassnacht (Würzburg),
Stefanie Hahner (Würzburg)
and **Martin Reincke** (Munich)

You can read a full obituary at
[www.eese-hormones.org/
about/inmemoriam.aspx](http://www.eese-hormones.org/about/inmemoriam.aspx).

Endocrine Aspects in Andrology

Heraklion, Crete, 13–15 March 2015

The programme covered a broad spectrum of basic and clinical aspects of andrological endocrinology. Among many highlights, the opening lecture by Ilpo Huhtaniemi (London) focused on 'Molecular aspects of gonadotrophin action', summarising cutting edge data.

Clinical presentations by leading experts covered hypogonadism, androgen replacement, androgen insensitivity, inflammation and sex hormones, Klinefelter and Kallman syndromes and testicular maldescent. Three oral presentations were selected to be given by young researchers, and all were very impressive.

The 80 participants were evenly divided between PhD students and senior

researchers. This relatively small number of participants and their multidisciplinary background created an intimate atmosphere and facilitated lively and nuanced discussions.

In Greece, as elsewhere in Europe, information about clinical andrology and associated research is in great demand. This symposium was, therefore, welcomed by the participants who requested a follow-up event in 2–3 years.

Much of the symposium will be available in the form of review articles in the journal *Hormones*. We thank ESE for generously providing an ESE Small Meeting Grant.

Maria Alevizaki, on behalf of the Organising Committee

The Future of Endocrinology

3rd EYES Meeting, Modena, Italy, 24–26 September 2015



The 3rd EYES Meeting was attended by 220 young endocrine scientists, demonstrating the growing interest of the young European community in EYES and ESE activities. Almost 200 abstracts were submitted from 32 countries.

Close collaboration between the EYES Board and the Italian young endocrine scientists' group EnGiol ensured the meeting's success. EnGiol (a committee within the Italian Society of Endocrinology) actively disseminates the 'voice of endocrinology' among young Italian scientists.

Young scientists were able to present their work relating to many endocrine disciplines, including diabetes and metabolism, bone metabolism, thyroid, pituitary and adrenal diseases.

They were particularly motivated by two presentations from senior scientists. Manuela Simoni, Chair of Endocrinology at the University of Modena and ESE Executive Committee member, shared her personal experience in endocrinology. She offered the young researchers advice about becoming successful scientists in the field.

Then, Brian Finan from the Helmholtz Centre in Munich, Germany, shared his seminal work on the discovery and application of novel incretin-

based pharmacological compounds for the treatment of metabolic diseases. As a young scientist with 'senior scientific achievements', Dr Finan was a great inspiration to the participants.

Carmina Teresa Fuss (Germany) received the EYES-ESE Award for the best presentation by a participant, which was on 'High expression of C-X-C chemokine receptor type 4 in the zona glomerulosa and in aldosterone-producing adenoma'. This includes the honour of presenting her work at ECE 2016 in Munich, during the EYES symposium.

We look forward to seeing you all at the 4th EYES Meeting, in Moscow, Russia on 22–24 September 2016. For further details, see <http://eyes2016.science.org.ru>.

Eyes
EUROPEAN
YOUNG ENDOCRINE
SCIENTISTS
looking forward

For further
information, contact
EYES@euro-endo.org
or see
www.es-e-hormones.org



ESE Summer School on Endocrinology

Bregenz, Austria,
2–6 August 2015

The Bregenz Monastery Mehrerau at Lake Constance in Austria was again the meeting place for young researchers and internationally renowned experts in endocrinology. A total of 76 participants, including MD and PhD students, postdoctoral researchers and senior scientists from 20 European and non-European countries, gathered in a friendly atmosphere with high level, informative lectures and interactive seminars.

The lively discussion after lectures and during poster presentations often continued during lunch and free time, creating an attractive environment for networking and learning about new techniques, animal models, hormone analysis, etc.

The Summer School gave participants the chance to hear and meet experienced



world class scientists, such as Guillaume Assié (Paris), speaking on the molecular basis of adrenal cancer, Paul Le Tissier (Edinburgh), on pituitary development, and Annika Herwig (Hamburg), on the role of thyroid hormone in regulating the daily torpor of hamsters.

Feedback indicates that the ESE Summer School was a big success yet again. We thank all participants and speakers for

their valuable input, and look forward to meeting you at a future event!

Rahel Büttler (Amsterdam),
Milena Doroszko (Turku),
Luis Cardoso (Coimbra),
Carolin Höfig (Stockholm)
and **Raffael Ott** (Berlin)

EYES and YARE (Young Active Research in Endocrinology) representatives



Building on a strong foundation

From your Science Committee

I have recently been entrusted with the prestigious position of Chair of the ESE Science Committee, and am keen that it continues to promote endocrine research in Europe. We are pleased to welcome two new Committee members, Maria Zatelli (Italy) and Marc Lombes (France), and would like to thank outgoing members Wiebke Arlt, Laszlo Hunyady and Ruben Nogueiras for their hard work and role in the achievements of the last 4 years.

The ESE Science Committee serves to support scientific research in endocrinology in Europe. It provides a voice for ESE members working in basic research, allowing their needs to be addressed. It is actively involved in ensuring that the programmes of training events, conferences and symposia meet the requirements of the research community. These activities will remain a priority throughout my term.

I encourage all ESE members who are interested and working in basic science to visit www.ese-hormones.org and read about the benefits available to them. These include exclusive travel grants to attend ECE, ESE Short-Term Fellowships to visit collaborators abroad, access to the ESE International Endocrine Scholars Programme, and more. You will also find information on training courses and events, as well as focused high level symposia on the latest research topics. These resources are especially useful for early career researchers seeking to establish themselves and stand out from their peers.

ESE has invited members of our Affiliated Societies to become ambassadors for European endocrine research. Through these ESE Science Ambassadors, the impact of our activities can be greatly increased. We encourage engaged endocrine researchers interested in increasing the visibility of ESE's basic

science activities to get in contact with their national societies for more details. Successful applicants will be invited to the ESE Science Ambassadors Committee meeting held annually during ECE. In this forum, Ambassadors will have the opportunity to put their ideas to the ESE Science Committee and be actively involved in Committee activities.

The Science Committee welcomes suggestions and ideas for further improving basic endocrine research in Europe. Please contact info@euro-endo.org.

I look forward to working with you over the next 4 years.

Márta Korbonits
Chair, ESE Science Committee

Clinical Committee Update

Creating equality of care



It is a real pleasure and honour to serve the ESE as Chair of the Clinical Committee. The Committee's aims are described perfectly at www.ese-hormones.org/about, but I would like to emphasise some of the major tasks that I will aim to undertake, with the assistance of the Committee members and the very efficient team in the ESE office. The active participation of Society members will be also very important in developing our activities.

One of our major objectives is to develop not just high quality but also equality in patient care across Europe. The development of ESE guidelines, which Pia Burman (the previous Committee Chair) initiated so efficiently, is an excellent way to reach this objective. Following the publication of the hypoparathyroidism guidelines, new guidelines are expected on pheochromocytoma, adrenal incidentaloma and Turner syndrome. We will work hard to guarantee a continuous production of such guidelines. Special interest groups are also important in allowing reflection on specific topics at the European level.

To achieve their objectives, effective communication of the guidelines and recommendations is essential, and ESE publications and the website have an important role to play. In the same spirit, the Committee will liaise with other areas of ESE, to develop education and training across Europe on clinical endocrinology,

not just for a broad range of healthcare professionals but also for patients.

I believe the Committee should have a role in developing those areas of clinical endocrinology that require a European dimension to make good progress. Various aspects of clinical research, such as development of international databases for rare diseases, will be the focus of these efforts. Along the same line, many endocrine disorders are, in fact, rare diseases. Linking enough experts across borders to develop, in a broadly visible manner, the various specific skills needed to diagnose and manage these disorders is crucial in improving patient clinical care and equality.

Jérôme Bertherat
Chair, ESE Clinical Committee

Endocrine disruptors: what is their full impact?

Scientific concern regarding the health impact of endocrine-disrupting chemicals (EDCs) has been growing rapidly in recent years, in parallel with mounting evidence linking developmental exposure to environmental chemicals with adverse health consequences.¹

The main body of literature on endocrine disruption is derived from wildlife observations, epidemiological data on humans, and laboratory research with cell cultures and animal models. All this evidence gathered together indicates a global problem whose biological implications for human health are complex and still under investigation. Nevertheless, it is obvious that contamination with EDCs is widespread in the atmosphere, leading to constant human exposure (though multiple routes). In some cases, this has been associated with diseases such as impaired reproductive function, increased birth defects and raised cancer prevalence.^{1,2}

What has not been thoroughly analysed so far is the possible economic impact of endocrine disruption on healthcare services. Recently published papers in *Journal of Clinical Endocrinology & Metabolism* provide significant information on the cost of EDC-related illness across the European Union.³⁻⁷

Assessing the financial burden

The authors' approach was based on well-documented epidemiological and toxicological evidence linking seven chemicals and chemical classes with three broad disease groups with a high probability of exposure-outcome causation. Scientists calculated the economic cost that could be reasonably attributed to specific EDC exposures in male reproductive disorders⁴ (infertility, cryptorchidism, testicular cancer, lower testosterone concentrations), selected neurobehavioural effects³ (IQ loss, autism spectrum disorders) and metabolic disorders⁵ (including adult/childhood obesity and diabetes).

Economic burden was evaluated as direct costs related to expenses for hospitalisation, physician services, nursing home care and other medical

fees, as well as indirect costs embracing lost worker productivity, premature death and disability.⁶ The outcomes of these studies are undoubtedly alarming, as the estimated median annual cost of endocrine disruption lies at €157 billion; when using the lowest probability, this falls to approximately €109 billion.⁶

A wake-up call?

These studies represent an important step forward in our ability to comprehend the health economic consequences of endocrine disruption. Despite their acknowledged limitations, including the relatively small number of chemicals examined and the effectiveness of the 'human capital approach' method to cost illness, these articles could act as a wake-up call for steps to control exposure to environmental chemicals.

For instance, aside from the apparent individual health benefits, prevention of exposure to certain EDCs may be an effective initiative to lower healthcare expenditure.⁶ Furthermore, the increased probability of neurodevelopmental deficits interestingly indicates a link to the detrimental effects of endocrine disruption in the sensitive developing infant/child^{1,3} and the hazards that this encompasses for future generations.

Fundamental questions

The findings of the aforementioned publications are alarming, and give rise to some important questions regarding our knowledge of endocrine disruption. Despite their conservative economic estimates, the numbers are undoubtedly impressive, leading to some rational questions.

- Do the identified health hazards related to EDCs represent only the tip of the iceberg for endocrine disruption?
- Are there other 'disasters' waiting to happen in the present or future generations?



- Which are the populations that are most susceptible to EDCs, and who should actually be afraid of them? The pregnant woman and her child? The healthcare professionals and authorities? Or the man next door?

- And finally, what are the next steps needed to prevent the oncoming economic and health 'catastrophe' – before it is too late?

Evanthia Diamanti-Kandarakis

Professor of Medicine – Endocrinology and Metabolism, Director, Department of Endocrinology and Centre of Excellence in Diabetes, Euroclinic, Athens, Greece



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GH influences adipogenesis of mouse mesenchymal stem cells



Growth hormone (GH) deficiency leads to increased fat mass, whereas GH excess is associated with a decrease in fat mass. In addition to the effects of GH on lipolysis, this might be related to effects of GH on adipocyte differentiation.

Mesenchymal stem cells (MSCs) derived from adipose tissue are multipotent and are able to differentiate into different cells, including adipocytes. This study by Olarescu *et al.* suggests that GH diminishes subcutaneous fat mass in part by altering adipogenesis of MSCs.

Read the full article in *Journal of Endocrinology* **226** 13–23

Side population in pituitary tumours exhibits stem cell characteristics



The mechanisms of pituitary adenoma pathogenesis have largely been unresolved.

Mertens *et al.* have described a side population in pituitary tumours of cells that display tumour stem cell molecular and functional characteristics. Identification of this cell population may ultimately enable us to better understand pituitary tumour pathogenesis.

Read the full article in *Endocrine-Related Cancer* **22** 481–504

Fructose in low calorie diets and cardio-metabolic risk factors



Low calorie diets (LCD) can induce meaningful weight reduction (5–10%) in short term interventions. Fructose is often added as a sweetener, but its intake is associated with adverse effects on cardiovascular metabolic risk factors.

Johnson *et al.* compared an 8-week low-fructose LCD with a traditional LCD based on fructose-rich liquid meal replacements. The diets (~4500kJ; fructose 6 vs 32 energy %) caused a weight loss of ~10kg in obese women with polycystic ovarian syndrome ($n=51$, BMI 43–44 kg/m²). Both diets induced considerable improvements in various cardiometabolic risk factors and reproductive hormones, with no differences between their effects.

Read the full article in *Endocrine Connections* **4** 144–154

Irreversible effects on the brain in Cushing's syndrome

Clinicians generally thought reversal of glucocorticoid excess resulted in virtually complete reversal of the characteristic symptoms. However, despite long term biochemical control, patients report decreased quality of life, and have a higher prevalence of psychopathology and impaired cognitive functioning.

This systematic review of MRI studies by Andela *et al.* shows that endogenous glucocorticoid excess has profound effects on the human brain, including structural grey matter, possible white matter and neurochemical and functional alterations. Abnormalities in both grey and white matter are not completely reversible at long term remission.

Visfatin in glucose uptake into skeletal muscle cells



Glucose transport in skeletal muscle is regulated by two pathways: stimulation by insulin and the insulin signalling cascade and stimulation by muscle contraction through the activation of AMP-activated protein kinase (AMPK). Both pathways increase the phosphorylation and activity of MAPK family components.

Lee *et al.* have shown that visfatin, an adipocytokine produced by different tissues, stimulates glucose uptake in skeletal muscle cells through the AMPK pathway. Taking previous publications into account, it is still too early to draw definite conclusions about the *in vivo* functions of visfatin at present.

Read the full article in *Journal of Molecular Endocrinology* **54** 251–262



These observations provide evidence for neurotoxic effects of glucocorticoids on the human brain.

Read the full article in *European Journal of Endocrinology* **173** R1–R14

J A Romijn

Editor-in-Chief of *European Journal of Endocrinology*, Department of Medicine, Academic Medical Center, University of Amsterdam, The Netherlands
j.a.romijn@amc.uva.nl

Insulin signalling, oncology and the impact of diet

Lewis Cantley (New York, NY, USA) spoke at ECE 2015 on PI 3-kinase and its role linking glucose metabolism, cancer and the Western diet. ESE President AJ van der Lely interviewed Professor Cantley after his talk, and we are delighted to summarise their fascinating discussion here.

LC: There is a correlation between obesity, diabetes, insulin resistance and some cancers, for example, endometrial, colorectal and breast cancers. It may be ambient serum insulin levels that really exacerbate this problem. The enzyme phosphatidylinositol (PI) 3-kinase is familiar to endocrinologists, as it mediates insulin's actions in liver, muscle and fat. But it is also one of the most highly mutated enzymes in cancer, and the tissues where you frequently find PI 3-kinase mutations are those that typically develop cancers correlating with obesity and diabetes.

When becoming obese, people tend to develop insulin resistance, perhaps leading to type 2 diabetes. The period of insulin resistance is most dangerous with regard to cancer, as insulin levels become very high, to mediate glucose homeostasis. Many cancers (especially those correlating with obesity) express high levels of the insulin receptor, and so the ambient high levels of insulin can drive activation of PI 3-kinase in the tumours. We think this is the cause of the correlation.

AJL: In your work, you found the mutations were the same in most cells, in contrast with the seemingly impressive intercellular variety often seen in tumours. Why is that?

LC: Most mutations in cancers are passenger mutations, which don't cause cancer but are the result of reactive oxygen stress. But if a mutation gives a cell an advantage, then that cell can take over the entire tumour by growing more rapidly. We can see that process as we develop techniques to sequence individual cells or areas within tumours. PI 3-kinase often exhibits a 'trunk' mutation: one that happened in the first cell that initiated the tumour, though sometimes it is a later 'branch' mutation, only present in a fraction of the cells.

AJL: Inhibitors of this signalling system are now emerging. How do you foresee their role?

LC: The first PI 3-kinase inhibitor to be approved inhibits the delta form of the enzyme. *PIK3CD*, which encodes p110delta, is expressed in haematopoietic cells, and T and B cell receptors both stimulate that enzyme. A drug targeting this form is very effective in chronic lymphocytic leukaemias.

However, that drug does not affect the PI 3-kinase that insulin stimulates. This is encoded by *PIK3CA* (p110alpha). Many drugs target this form, or are pan-inhibitors, targeting all the forms; these drugs cause an acute insulin resistance (an on-target effect), while delta-specific drugs don't.

AJL: Treatment of these tumours must require the lowest possible insulin activity. How can clinicians achieve that? It will induce huge hyperglycaemia.

LC: This is a problem. Type 2 diabetics are excluded from trials of the alpha- and pan-inhibitors as it is so difficult to control glucose levels. There is a growing obese population, and a typical patient on these trials will be a breast cancer patient in their late 50s, many of whom have borderline insulin resistance.

In some cases, an endocrinologist will recommend going on insulin, but that could exacerbate the problem. If you provide enough insulin to overcome inhibition of PI 3-kinase in fat, liver and muscle it is probably enough to overcome inhibition of the PI 3-kinase in the tumour, assuming the tumour is driven by an insulin receptor, which isn't always the case. In future, we must determine the insulin receptor status at the outset, as patients whose tumours express the



receptor must be managed much more acutely than those whose tumours don't, to keep insulin low.

AJL: Intake of glucose and especially fructose is increasing hugely in the Western world. What is fructose's role in this field?

LC: Fructose is our enemy. The liver handles it very differently from glucose, quickly clearing it from the bloodstream, so it doesn't reach muscle or brain, or provide any immediate energy benefit. Once in the liver, fructose is hydrolysed immediately by aldolase and enters glycolysis to be stored as fat. This is in contrast to glucose, which can be stored as glycogen if there are high ATP and citrate levels.

It may appear healthy to eat fructose as it is a low glycaemic sugar but, after some time, massive consumption leads to fatty liver, which can cause insulin resistance and type 2 diabetes. Eating glucose, of course, gives an insulin spike that makes you hungry an hour later (so leading to overeating). The worst possible thing to eat is a mixture of fructose and glucose, which is exactly where the Western diet is heading. In general, keeping rapid release carbohydrates low in the diet is best.

You can see the full interview and other highlights at www.ece2015.org.

Endocrine disruptors: a recent issue?

The term 'endocrine disruptor' was coined in July 1991 in a statement by Howard A Bern (1920–2012) and colleagues, reporting on a work session on 'chemically induced alterations in sexual development: the wildlife/human connection' held in Racine (WI, USA). Professor Bern was Professor of Integrative Biology and a research endocrinologist at the Cancer Research Laboratory at the University of California at Berkeley (CA, USA).



However, people had been noting the environment's impact on endocrine systems for many years before Bern's statement. For centuries, farmers had observed reproductive problems in ewes and cows feeding on grazing lands rich in certain clover species. In the first half of the 20th century, it had already been discovered that these plants were rich in oestrogenic compounds. In the USA, an outbreak of thyrotoxicosis caused by consumption of ground beef prepared from neck trimmings containing bovine thyroid tissue and high concentrations of thyroid hormone occurred between spring 1984 and autumn 1985.

PCBs, dioxins and public health

The impact of industrial pollutants had also been recognised for some decades. (Congeners of) polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) can act on the oestrogen and arylhydrocarbon receptors and/or modulate thyroid hormone levels, metabolism and actions. In 1968, a mass poisoning by PCBs occurred in northern Kyūshū in Japan and was named 'Yushō disease'. Eleven years later, in 1979, a similar tragedy happened in Taiwan and was named 'Yu-cheng disease'. Thousands of women were exposed to PCBs and PCDFs, and the offspring of these mothers tended to be smaller at birth and exhibited delays in neurological development. More recently, in 2008, a dioxin contamination incident in Ireland led to an international recall of Irish pork products.

Landmark publications

In wastewater outlets in the USA, the presence of hormones and other pharmaceutical agents was noted as early as the 1960s. In 1962, Rachel L Carson (1907–1964), a renowned American nature author and former marine biologist with the US Fish and Wildlife Service, published her bestseller *Silent Spring*. In this, she documented the detrimental effects of the indiscriminate use of pesticides, especially dichlorodiphenyltrichloroethane (DDT), on the environment. The book was met with fierce opposition by chemical companies, but it eventually led to a nationwide ban on DDT and other pesticides, and to the creation of the US Environmental Protection Agency.

However, endocrine-mediated toxicity initially did not gain more attention, since it was regarded as just one of many potential mechanisms that could lead to certain negative effects.

Over three decades later, in 1996, another blockbuster publication *Our Stolen Future: Are We Threatening Our Fertility, Intelligence and Survival? A Scientific Detective Story* was published by the American author Theodora E Colborn (1927–2014), Professor Emeritus of Zoology at the University of Florida at Gainesville (FL, USA), in collaboration with Dianne Dumanoski and John Peterson Myers, with a foreword from then US Vice President, Al Gore.

This book systematically reviewed the development of the endocrine disruptor hypothesis and suggested that pesticides

and other man-made chemicals were threatening the reproductive capability and intelligence of future generations of humans and wildlife. Theodora Colborn was Founder of The Endocrine Disruption Exchange (TEDX; www.endocrinedisruption.org), a non-profit organisation dedicated to compiling and disseminating the scientific evidence on the health and environmental problems caused by endocrine disruptors.

Looking to the future

In 2007, the report *Toxicity Testing in the 21st Century: a Vision and a Strategy* was published by the US Committee on Toxicity Testing and Assessment of Environmental Agents for the National Research Council of the National Academies of the USA. It examined how laboratory tools could be used to understand the hazards and risks posed by chemicals and so lead to better informed environmental regulations.

The most recent European Commission conference on 'Endocrine Disruptors: Current Challenges in Science and Policy' took place in June 2012. Its aim was to inform the European Commission's strategy on endocrine disruptors and their criteria for identifying these substances.

So, it is almost a quarter of a century since the term 'endocrine disruptor' entered the language, though the concerns date back long before then. Recognition of the associated endocrine issues continues to increase worldwide, and they are set to grow greatly in scope.

Wouter W de Herder

Erasmus MC, Rotterdam, The Netherlands

A Day in the life of...

An endocrinologist studying pollution's impact on health

06.45

Good morning! I start my day by checking new emails, the news and weather on my mobile. The weather forecast is crucial if you go to work on a two-wheeled vehicle; even Sicily is not always sunny and the weather can suddenly change.

08.00

After a light breakfast of espresso and brioches, I go to the university hospital by scooter. Several patients are already waiting at my office door, but often only half have arranged appointments. Unfortunately, this behaviour is common practice for some people, although rarely justified by an emergency. It is probably also our fault because, with the help of the PhD fellows and trainees, their requests are generally satisfied.

09.00

The start of the day is usually dedicated to managing the ward of our Endocrine Unit. It is relatively small, but well organised in a single department with the Allergology and Rheumatology Units. Patients are admitted on Monday or Wednesday and are discharged no later than the following Friday, as our ward is closed for the weekend. Recently, the continuous arrival of North African migrants has seen their admission to our department, as it is near the Units of Infectious and Respiratory Diseases. The emergency situation dramatically decreases the availability of beds in all Sicilian hospitals. Although most people in southern Italy show great solidarity and generosity, this predicament is extremely stressful for our regional healthcare system, especially in a period of financial crisis.

11.00

After another espresso with some of my PhD fellows or trainees, it is usually time for a 2-hour lesson for students of the Medical, Dietetics or Radiology Assistant Schools.

13.00

At our regular meeting, we discuss the cases evaluated this morning and consider tomorrow's new patients. Each case is assigned to a trainee, who follows them closely from admission to discharge, and presents their history and management to other colleagues.

14.00

It's lunchtime, but first I call surgeons and neurosurgeons to discuss patients who were operated on for adrenal masses or pituitary adenomas in the last few days. Sometimes I also visit these patients, assisted by one or two trainees. Our university



hospital is a referral centre for pituitary and adrenal diseases in southern Italy and each month sees several operations. A cyber-knife centre and nuclear medicine facility for complementary treatment of aggressive pituitary tumours are also available. I am delighted to work with a team of skilled surgeons, radiologists, ophthalmologists and radiotherapists, each of whom we have trained step by step.

15.00

The afternoon is dedicated to scientific research and writing papers. Recently, we have focused on the effects of environmental pollution on pituitary tumorigenesis. A link was suggested by the large number of acromegalic patients from polluted areas of Sicily, where the prevalence of the disease reaches about 210 cpm. Increasing evidence for the role of xenobiotics in pituitary tumorigenesis is emerging, through the research of our team and other Italian groups, sustained by a grant from the Department of Scientific Research of the Italian Government.

19.30

I return home, hoping my kids are keen to talk about their day, but I discover they have gone to a party and will come back late. Fortunately, Sicilian food, prepared by my wife for dinner, is very good and a sufficient reward for the day's efforts.

21.00

I still have to prepare a presentation for the next congress on pituitary diseases, to check some documents, to pay bills online and to reply to tons of emails. It was probably better when computers did not exist and we ended the day reading a good book!

00.30

My kids are back. I switch off my computer and finally I can go to bed. Good night!

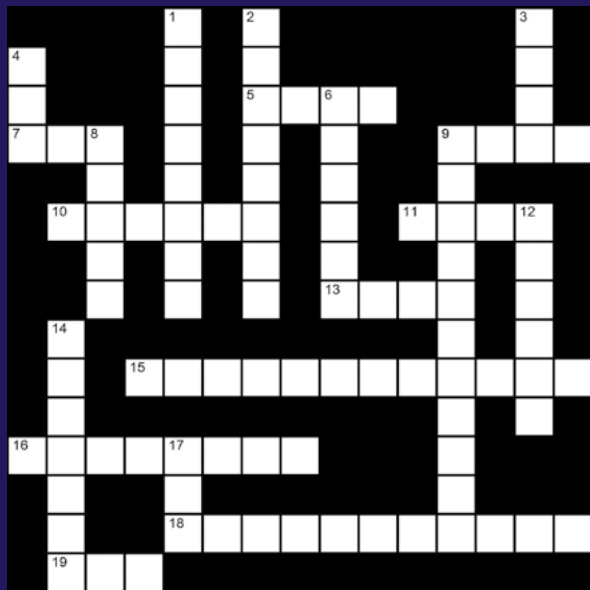
Salvo Cannavò

Department of Clinical and Experimental Medicine, Endocrine Unit, University of Messina, Sicily, Italy



**WIN!
WIN!
WIN!**

Send us your solutions to this topical puzzle for your chance to win one of three €20 Amazon vouchers! Let us have your answers, along with your name and email address, by emailing them to info@euro-endo.org or faxing them to 0044 1454 642222.



Congratulations to Jurij Hanzel (Slovenia), Aura Reghina (Romania) and Kuljinder Singh Jandu (UK), winners from issue 26.

Answers to the puzzle in issue 26

ACROSS 1. Patrick, 6. CRISPR, 9. BMI, 12. Walton, 13. Dublin, 14. Green, 15. James Joyce
DOWN 1. PTH, 2. Trinity, 3. Cork, 4. AIP, 5. Addison's, 7. Robert Boyle, 8. Fungus, 10. Guinness, 11. Graves'

Endo Prize Puzzle

Across

- 5 Mutational hotspot in Cushing's, affecting EGF receptor (4)
- 7 Synthetic insecticide developed in 1940s (abbrev.) (3)
- 9 Porphyrin-based cofactor in erythrocytes (4)
- 10 Location of 1976 major accidental dioxin release (6)
- 11 Divalent ion, bound to 9 across (4)
- 13 Cleaved from POMC, excess causes Cushing's (abbrev.) (4)
- 15 Egg yolk precursor protein, biomarker for environmental oestrogens (12)
- 16 To adapt from fresh water to sea water, in fish (8)
- 18 Thyrotoxic pollutant, used to make explosives (11)
- 19 Cleaved from POMC, in response to UV (abbrev.) (3)

Down

- 1 Spermatozoon (8)
- 2 Monosaccharide, 'fruit sugar' (8)
- 3 Release is stimulated by cholecystokinin (4)
- 4 Androgen insensitivity syndrome, for example (abbrev.) (3)
- 6 Gene: insulin stimulates this phosphatidylinositol 3-kinase (6)
- 8 Humans exhibit 20 at the age of 3 (5)
- 9 *In vivo* assay for endocrine disruptors in castrated mammals (11)
- 12 Vitamin, nicotinic acid (6)
- 14 Toxic metal, causes osteomalacia and osteoporosis (7)
- 17 Essential amino acid, codon UGG (abbrev.) (3)

Did you know?

The famous Dr House (played by Hugh Laurie) has an excellent knowledge of endocrinology!

In episode 116 'Heavy' (first broadcast 29 March 2005), a 10-year-old obese girl is referred after suffering a heart attack on the playground at school. Dr House's final diagnosis is Cushing's disease and the patient is cured by pituitary surgery.

Then, in episode 209 (first broadcast 13 December 2005), Dr House diagnoses a woman with Munchausen syndrome, because this patient fakes Cushing's syndrome by injecting herself with adrenocorticotrophin.



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17th ESE Postgraduate Course on Endocrinology, Diabetes and Metabolism

19-22 November 2015
Tirana, Albania

7th ESE Clinical Update

15-16 January 2016
Abu Dhabi, UAE

ESE Basic Course on Endocrine and Neuroendocrine Cancer

17-19 February 2016
Porto, Portugal

18th ESE Postgraduate Course on Endocrinology, Diabetes and Metabolism

25-28 February 2016
Opatija, Croatia



18th European Congress of Endocrinology (ECE 2016)

28-31 May 2016
Munich, Germany

19th European Congress of Endocrinology (ECE 2017)

20-23 May 2017
Lisbon, Portugal

Deadlines:

30 November 2015
ESE Short-Term Fellowships
– application deadline

31 December 2015
7th ESE Clinical Update
– call for cases

14 January 2016
ESE International Endocrine Scholars Programme (IESP)
– application deadline

1 February 2016
ECE 2016 – abstract deadline

28 March 2016
ECE 2016 – early bird registration deadline