

Issue 41 Winter 2019/20

ESE News

The newsletter of the European Society of Endocrinology

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ECE in Prague

For the very latest in endocrinology

Also in this issue

Czech endocrine research
New ESE obesity guideline



European Society
of Endocrinology



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Editorial



The arrival of a new year means only one thing – it's time to submit your latest research to the next European Congress of Endocrinology. The abstract submission deadline of 3 February is fast approaching! Prague, capital of the Czech Republic, is set to provide an excellent backdrop for our deliberations this May, as it did a decade ago.

As the Programme Organising Committee (POC) Co-Chairs say on page 8, 'The "key" speakers will, of course, be you and me, and the backbone of the programme is, as always, made up of abstracts submitted by dedicated clinicians and scientists.' Thanks are due to Attila Patócs and Jens Otto Jørgensen, along with the rest of the POC, for compiling an excellent programme. It not only spans all ESE's eight Focus Areas, it also accommodates the needs of ESE's communities, such as the Society's nurses and early career members.

The Congress and Czech endocrinology provide the theme for this issue of *ESE News*. We are privileged to have insights from our award lecturers on page 9. On page 3, Michal Kršek and Jan Jiskra provide a warm welcome to Prague on behalf of the hard-working Local Organising Committee and the Czech Society. Sherwin Criseno (Nurse Committee Chair) and the ESE Young Endocrinologists and Scientists (EYES) give us a flavour of what's in store for their groups on pages 6 and 7 respectively.

The 3rd Department of Internal Medicine at Charles University in Prague has played a central role in the development of endocrinology in the Czech Republic. On page 10, the Department's current members reflect not only on their many active areas of research, but also on the work of their predecessors, who established an enviable reputation.

Very sadly, one of those predecessors, a familiar and well-respected face in European endocrinology, will not join us at ECE 2020. We are honoured that Josef Marek's last article, written in the weeks before his final illness, was for *ESE News*. His brief history of Czech endocrinology appears on page 14.

Finally in our journey through Czech endocrinology, Martin Haluzík takes us on an action-packed day in his life as an endocrinologist/diabetologist on page 15. As he combines clinics, teaching, grant applications, his role as an Editor-in-Chief, family life and the trauma of European football, there is sure to be something with which you will identify!

As well as all this, we welcome a new ESE Clinical Practice Guideline, on the endocrine work-up in obesity. We thank and congratulate Renato Pasquali and the Guideline Working Group; you will find details on page 12.

Justo P Castaño
Editor, *ESE News*

Cover image: Victory driving a triga (three-horse chariot), on Prague's National Theatre, by Czech sculptor Bohuslav Schnirch (1845–1901).
© Shutterstock/prokoole



Key dates

Submit your abstracts by:

Monday 3 February 2020

Early bird registration closes:

Wednesday 8 April 2020

www.ece2020.org



Come to Prague!

22nd European Congress of Endocrinology, 23–26 May 2020

It is my privilege and pleasure to invite you to Prague, capital of the Czech Republic, for the 22nd European Congress of Endocrinology. Almost exactly 10 years since ECE 2010, which was very successful (despite travel disruption caused by the memorable ash cloud from the Icelandic volcano Eyjafjallajökull), we will return to the same venue – the Prague Congress Centre – just a few minutes from the historic city centre. As well as having a large variety of halls and conference rooms, with the latest equipment, it also provides an incredible panoramic view over the city.

Prague offers the very best of both the historical and the modern: hotels, restaurants, infrastructure and places of interest. Importantly, this famous city is located in the very heart of Europe, and can be easily reached from locations all over the world.

This is a historical city, not only culturally, but also from a scientific perspective. I must mention the famous physiologist, biologist and philosopher Jan Evangelista Purkyně (1787–1869), who is known for many discoveries in medicine,



and Ján Jesenský (Jessenius, 1566–1621), who performed the first autopsy in 1600.

Josef Charvát (1897–1984) is considered the founder of Czech endocrinology, as well as of the 3rd Department of Internal Medicine of Charles University in Prague, which remains the leading centre for endocrinology in the Czech Republic. Karel Šilink (1905–1973), the founder of the Institute of Endocrinology in Prague, was another famous endocrinologist of that time. They were followed by many famous and world-renowned endocrinologists, including (amongst others) Vratislav Schreiber, Otto Küchel, Luboslav Stárka and Josef Marek.

Private endocrinologists working on an outpatient basis provide the cornerstone of endocrine care in the Czech Republic. Complicated cases are managed in tertiary centres associated with the network of University Hospitals located

in the cities of Prague, Pilsen, Hradec Králové, Brno, Olomouc and Ostrava. Endocrinologists in the Czech Republic can mostly be counted among the more than 450 members of the Czech Society of Endocrinology.

I strongly believe that the tradition of Czech endocrinology, the history and beauty of Prague and the hard work of the Programme and Local Organising Committees will result in an excellent and successful Congress, which is sure to attract a high attendance. I cordially invite you to Prague on behalf of the Local Organising Committee and the Czech Society of Endocrinology, and look forward to seeing you next May.

Michal Kršek

Local Organising Committee Chair, ECE 2020
President, Czech Society of Endocrinology

Welcome from the Czech Society

The Czech and Slovak Societies of Endocrinology were founded in 1938, as the Czechoslovak Society of Endocrinology. Since then, these Societies have played an important role in the development of our discipline in both the Czech and Slovak Republics.

Czechoslovakia's division into the Czech and Slovak Republics in 1992 saw the foundation of the two separate societies, which still co-operate closely. Even behind 'the Iron Curtain', solid research took place in Czechoslovakia. After the breakdown of communism, research proceeded with growing intensity.

We had 462 members at the end of 2018 and our membership is growing annually. We are a National Affiliated Society of ESE and our members are also members of the International Society of Endocrinology.

The Society supports young researchers through travel grants, and annually makes awards for the best published national work. We organise an annual national congress in collaboration with the Slovak Society of Endocrinology, and many smaller meetings and workshops with other societies.

Amongst our broad range of research activities, the National Register of Sellar Tumours (RESET) was founded in co-operation with Slovak Society of Endocrinology, and we are participating in a national project to evaluate universal thyroid screening in pregnancy.

All members of our Society recall the wonderful 12th European Congress of Endocrinology in Prague in 2010. We welcome you for an equally successful ECE 2020!

Jan Jiskra

Secretary, Czech Society of Endocrinology



Improving patient referral

The procedure for referral of patients from primary care to the endocrinology unit formed the focus of the 3rd Early Career Clinical Endocrinologists (ECCE) Meeting in Antalya, Turkey, on 24 October.

This 1-day event was organised by the ESE Council of Affiliated Societies (ECAS), and welcomed 19 early career participants, from 18 countries, with representation from the ESE Young Endocrinologists and Scientists (EYES).

As well as examining early career clinical endocrinologists' expectations and hopes regarding referral procedures, the event also considered the challenges and obstacles they face. They identified several areas with the potential for advancement, as follows. These may inform future collaborative work between the National Affiliated Societies and ESE.

1. Better education of primary care physicians regarding referrals:

- to inform general practitioners (GPs) of the full spectrum of diseases that endocrine units can treat and
- to explain to GPs when and when not to refer patients with endocrine disease.



Attendees at the 3rd ECCE Meeting

2. Organisation of clinical programmes such as:

- focused short courses on endocrinology for non-endocrinologists
- Continuing Medical Education programmes for GPs who deal with diabetes and other prevalent endocrine diseases
- joint clinics between primary care providers and specialists, in endocrine units
- educational activities that include patients/patient groups
- guidelines specifically for GPs who deal with endocrine cases and

- inclusion of a section on 'referral to the endocrine unit' in all ESE or National Affiliated Society guidelines.

3. Better communication between primary care and endocrine units, by means of:

- universal electronic record-handling for all patients with endocrine disease
- a system for e-communication between primary care and endocrine units and
- centres of excellence or special interest, to manage rare or complicated cases.

4. Practical proposals for referrals:

- they must be uniform (e.g. on standard forms) and
- they must fulfil 'minimum requirements', with all necessary information recorded.

The 4th ECCE Meeting will take place in Antalya, Turkey in October 2020. It will focus on 'Use of decision support systems in endocrinology'.

Dimitrios Goulis, Marija Pfeifer, Bulent Yildiz and Djuro Macut (as ECAS Representative to the ESE Executive Committee)

EndoBridge celebrates its 7th year

Antalya, Turkey, 24–27 October 2019



The 7th EndoBridge Meeting took place on 24–27 October 2019 in Antalya, Turkey, co-hosted by ESE and the Endocrine Society, in collaboration with the Society of Endocrinology and Metabolism of Turkey.

The meeting welcomed 680 delegates from 41 countries and included over 100 case presentations.

EndoBridge President Bulent Yildiz commented, 'The meeting once again provided

excellent opportunities for learning, collaboration and networking in a welcoming environment.' The 3-day programme included lectures by world-renowned experts and interactive discussions of

challenging clinical cases from across the field.

The 8th EndoBridge Meeting takes place in Antalya, Turkey, on 22–25 October 2020. More details will be available at www.endobridge.org.



New ESE Online Curriculum

The ESE Education Committee compiled the first *ESE Recommended Curriculum of Specialisation in Clinical Endocrinology, Diabetes and Metabolism* in September 2016. As well as providing students with a resource to assess the progress of their training, the Curriculum supports education providers in the development of content. It works towards a standard for endocrine education across Europe.

The Education Committee recently reviewed the Curriculum, to ensure it remains relevant and appropriately reflects the content of this clinical field. You can find the newly revised version at www.eese-hormones.org/education/eese-curriculum-of-specialisation.

To help endocrinologists-in-training access information and training resources, this revision is accompanied by the launch of the **ESE Online Curriculum**. This provides users with links

to resources for each of the curriculum topics, including the ESE Clinical Practice Guidelines, recorded content from the ESE Postgraduate Courses and the European Congresses of Endocrinology, and other relevant external online resources (PubMed, Clinical Trials and the European Medicines Agency).

In the coming months, the Education Committee aims to further develop the online educational resources for members, with material such as



interactive questions to allow members to test their knowledge on key topics.

You can start using the ESE Online Curriculum now at www.eese-hormones.org/education/eese-curriculum-of-specialisation/eese-online-curriculum.

European Board Exam 2020

The next European Board Exam will take place on 10 June 2020. Prospective candidates must register between 19 February and 18 March. You can sit the exam at various centres across Europe. For full details and applications, see www.ebeedm.eu.

ESE members may apply for a grant to cover 50% of the exam fee. See www.eese-hormones.org/grants-and-awards/grants for details. You will also find an online practice paper at www.eese-hormones.org/education/european-board-examination/sample-european-board-exam.

From the ESE Office

I write this having recently returned from the 13th Meeting of the ESE Council of Affiliated Societies (ECAS), which took place on 29 November in Milan, Italy. There was senior representation there from 30 national endocrine societies, who are all members of ESE as National Affiliated Societies. Overall, through our National Affiliated Societies, ESE represents around 22 500 endocrinologists across Europe. The meeting was chaired by ESE President Andrea Giustina, and the ECAS representative on our Executive Committee, Djuro Macut.

The discussions were diverse and interesting, and focused on our policy and advocacy priorities for the coming years. A new ESE representative membership proposal was discussed, which will allow us to more legitimately represent our European members within the policy and advocacy environment. It will facilitate real two-way engagement, to ensure that the direction we are taking



Attendees at the 13th Meeting of the ESE Council of Affiliated Societies

has the 'buy-in' of European endocrinologists on as broad a base as possible.

It felt like the beginning of a new chapter in our relationship with endocrinologists throughout Europe. Although there is work to do in finalising exactly what the new arrangements look like, the impression obtained from the meeting was that the principles around the scheme were very much welcomed, as was ESE's role in carrying out policy and advocacy work on behalf of the national societies. More will follow on this topic in the coming months!

Last time I wrote for *ESE News*, abstract submission for ECE 2020 was already open. Now registration has opened too, so our meeting in Prague next May is really coming over the horizon quickly!

Remember the 3 February 2020 deadline for abstract submission, and the early bird registration deadline of 8 April 2020. You can read much more about the Congress on the pages of this issue. Full details, including online abstract submission and registration, can be found at www.ece2020.org.

I can always be contacted with your comments and ideas at helen.gregson@ese-hormones.org. It would be great to hear from you!

Helen Gregson
Chief Executive Officer, ESE





Expanding the space for guidelines

From the Clinical Committee



The development of clinical guidelines for the optimal treatment of patients with endocrine disorders has been one of the ESE Clinical Committee's major responsibilities for many years. As the committee's new Chair, I am looking forward to contributing to this important activity.

Since 2015, seven ESE guidelines have been published (www.ese-hormones.org/publications/guidelines). The Clinical Practice Guideline on Endocrine Work-up in Obesity, led by Renato Pasquali (Italy), has just joined the list. This guideline was first presented at ECE 2019. After a careful and transparent process, in which all ESE members had a chance to review and comment on the draft, the final version is now available in *European Journal of Endocrinology*. You can read more about it on page 12 of this issue.

Guidelines for 2020 and 2021 are in preparation, and will cover 'Pituitary dysfunction during pregnancy' and 'Endocrine side-effects of checkpoint inhibitors/targeted cancer therapies' respectively. Over the coming years, we will not only continue to produce high quality guidelines, but also revise and update

the current guidelines, when appropriate.

In line with the 'Inclusion strategic plan' launched by our President Andrea Giustina in 2019, we will further explore the possibility of collaboration on joint guidelines with other relevant parties. We will also focus on increasing access to the ESE guidelines by additional means, such as guideline podcasts and mobile apps.

All these activities will help to additionally advance ESE's role as a global player in endocrinology, and continue to improve the care of patients across Europe and beyond.

Robin Peeters
Chair, ESE Clinical Committee

ESE guidelines

Endocrine work-up in obesity (2020)

Management of adrenocortical carcinoma in adults (2018)

Management of aggressive pituitary tumours and carcinomas (2018)

Care of girls and women with Turner syndrome (2017)

Management of adrenal incidentalomas (2016)

Long term follow-up of patients operated on for a pheochromocytoma or a paraganglioma (2016)

Treatment of chronic hypoparathyroidism in adults (2015)

Functioning pituitary tumours and gender dysphoria

Nurses at ECE 2020

We are delighted to present an exciting programme for endocrine nurses at ECE 2020 in Prague.

Four sessions for nurses are scheduled for Sunday 24 May. They will focus on evidenced-based assessment and management of functioning pituitary tumours and gender dysphoria, as well as providing the chance to learn from a nurse expert. A dedicated session will also support nurses' continuing professional development. These sessions will be followed by our popular annual nurses' networking event.

Functioning pituitary tumours and gender dysphoria are two complex and often challenging areas of endocrine practice. Our sessions will highlight the importance of multidisciplinary working and will include specialist nurses, patient

speakers, an endocrinologist, a radiologist and a psychologist. The aim is to explore the complex nature of these conditions and the important role that each member of a multidisciplinary team plays in providing the best possible standard of care.

To highlight the unique role of nurses in endocrinology, we are proud to welcome Andrew Dwyer (Switzerland) as our nurse expert, who will discuss sexual development and fertility in men.

Finally, counselling skills, presentation skills and the best approach to writing a clinical guideline will be the focus of our session on continuing professional development.

If this wasn't enough, we will once again hold a pre-Congress event, starting at 12.30 on Saturday 23 May at the Congress venue; access is free to those attending ECE 2020.



It will highlight developments in endocrine diagnostics, therapeutics and research in three key areas: growth hormone deficiency, bone and calcium disorders and rare endocrine conditions.

At this event, we will also continue our successful collaboration with patient organisation WAPO (the World Alliance of Pituitary

Organisations), as expert patients and endocrine nurses provide guidance to patients and patient advocates about establishing patient support groups.

You will be able to find further information and register for ECE 2020 at www.ece2020.org. We look forward to welcoming you to our sessions for nurses in Prague.

Sherwin Criseno
Chair, ESE Nurse Committee

You can find out more about the support offered by ESE to endocrine nurses at www.ese-hormones.org/about-us/our-communities/nurses.



It's time to grow out of endless growth

EYES at ECE 2020

We are delighted to invite you to join us at the 8th ESE Young Endocrinologists and Scientists (EYES) Symposium during ECE 2020 in Prague, on Monday 25 May.

Entitled 'It's time to grow out of endless growth', the symposium will focus not on economic growth, but on endocrine control of growth. It will include outstanding presentations by leading early career investigators from across Europe. Nikolaos Nikolaou (Greece/UK), who gave the best oral presentation at the recent 8th EYES Annual Meeting in Athens, Greece, will discuss the latest research on aldo-keto reductase 1D1 (AKR1D1) as a novel regulator of metabolic phenotype in hepatocytes in patients with non-alcoholic fatty liver disease. Three other promising early career researchers will join him on stage.

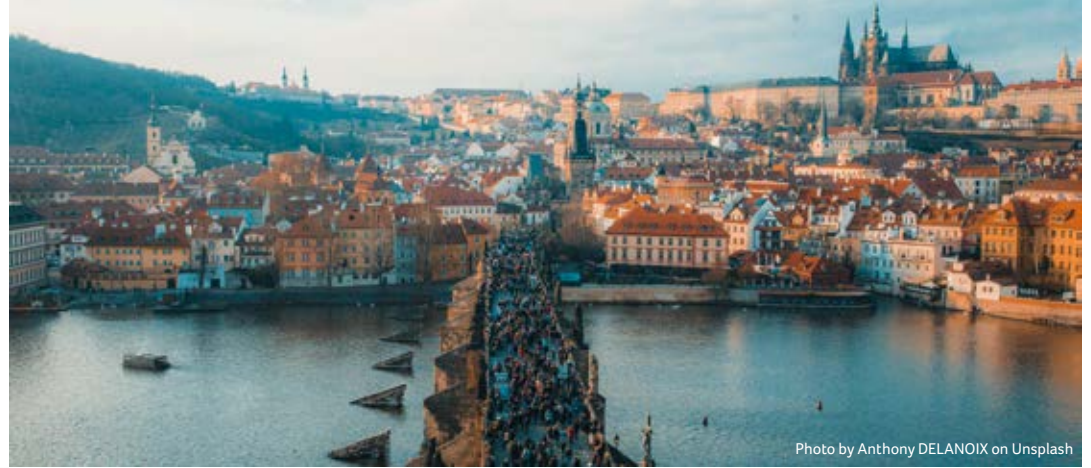


Photo by Anthony DELANOIX on Unsplash

This symposium will give you the chance to immerse yourself in a stimulating scientific environment, and will promote communication between subspecialties within endocrinology in an informal setting.

The friendly EYES community provides a great platform for potential collaborations between

early career investigators. There will be an informal opportunity to meet and establish links with colleagues at the now famous EYES networking event, the details of which will be announced at the symposium.

This invitation extends to ESE early career members and non-members, the EYES community and alumni, and those of you who

are young at heart. Whether you are a new endocrine enthusiast or a giant in your field, we invite you to join us at the 8th EYES Symposium to see the bright future of endocrinology. We look forward to seeing you in Prague!

Eva Coopmans and Filip Gabalec
Chairs, 8th EYES Symposium

A thriving community

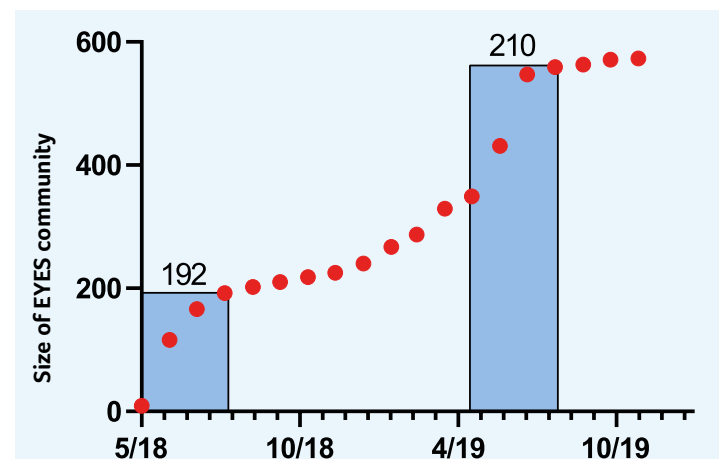
At ECE 2018, we decided to launch the official website for members of the EYES community (www.membermojo.co.uk/eyes). This was prompted by a need to record and keep in touch with everyone who joins EYES, bringing us all closer together.

So, how has it gone? Well, the website has had a huge impact in terms of engaging members of the EYES community, both old and new, with the release of a regular EYES newsletter distributed through our (now official) mailing list.

A quick look at the growth of EYES over the first 18 months is also exciting. Now more than 500 strong, our community has official members from all areas of endocrinology, across Europe. And ECE's importance is clear to see: that time of year sees our greatest rate of new joiners (see the blue bars on the Figure). A huge thank you is due to all at

ESE and EYES who work tirelessly to promote EYES and push us forward: keep up the good work!

A closer look at members of the EYES community shows that they are primarily clinical (~86%), split across clinicians (both in- and post-training), clinical fellows and clinical PhD students. It therefore stands to reason that EYES should continue to work hard as the driving force for the next generation of endocrinologists. However, we must also engage and maintain other groups, including basic scientists and clinical dietitians, and encourage people to join us across many countries, to ensure diversity.



Expansion of the EYES community since May 2018. Blue bars show rapid growth around the time of ECE 2018 and 2019

It's been a hugely productive 18 months for us, with another successful EYES Symposium at ECE, and an exciting EYES meeting in Athens, where 200 delegates represented 32 countries (up from 15 countries

just 5 years ago). The next 18 months should prove just as exciting, and we look forward to sharing them with you.

Peter Aldiss
EYES Committee



Key dates

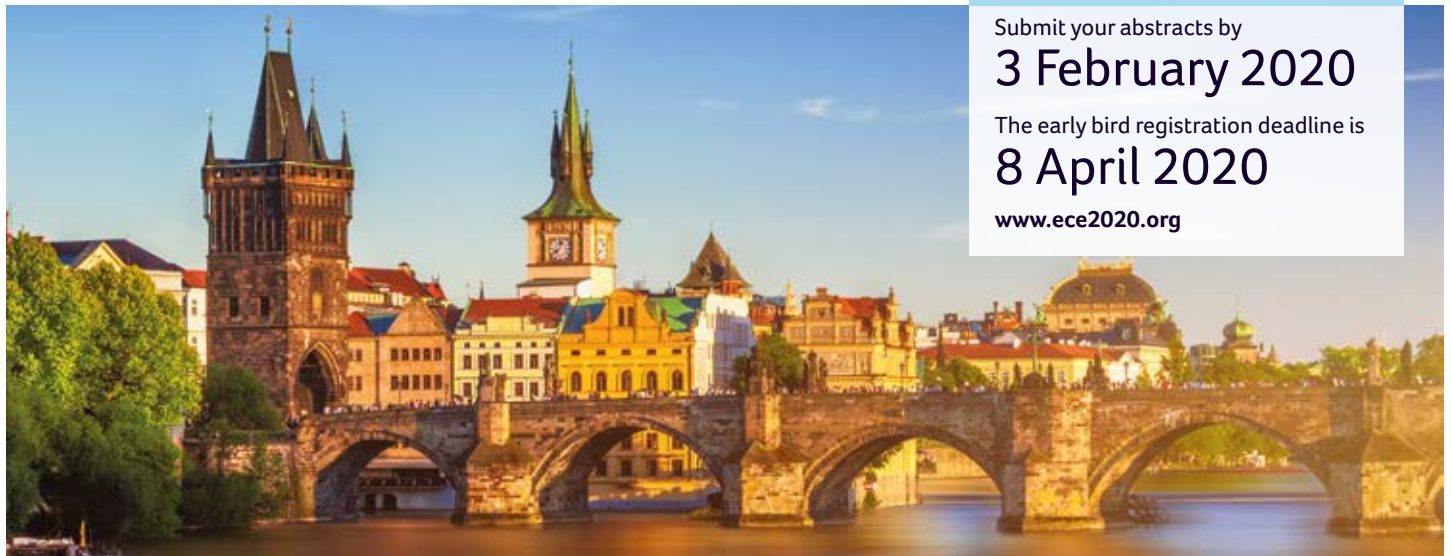
Submit your abstracts by

3 February 2020

The early bird registration deadline is

8 April 2020

www.ece2020.org



ECE 2020: bridging the gaps

Prague, Czech Republic, 23-26 May 2020

The success of ECE continues, and we are excited to welcome you to this year's Congress. With the combination of an innovative scientific programme and a magnificent venue, we hope you will join us to create new records.

In times of isolation and separatism, the ideals of science must shine brightly as a candle in the dark. It therefore makes so much sense to get together in real life and exchange scientific data and new ideas with an open-minded and friendly – yet critical – spirit. ECE provides the perfect opportunity to do exactly this.

The 'key' speakers will, of course, be you and me, and the backbone of the programme is, as always, made up of abstracts submitted by dedicated clinicians and scientists.

On top of this, the Programme Organising Committee has put together an attractive programme around ESE's eight dedicated Focus Areas:

- Adrenal and neuroendocrine tumours
- Calcium and bone
- Diabetes, obesity and metabolism
- Environment, society and governance
- Interdisciplinary endocrinology
- Pituitary and neuroendocrinology
- Reproductive endocrinology
- Thyroid

Award and plenary lectures

Come, celebrate our award recipients, and listen to plenary talks from experts in the following fields:

- Postmenopausal osteoporosis
- Rare diseases and autoimmunity
- Endocrine-disrupting chemicals and neuroendocrine disorders
- The present and future of neuroendocrinology
- Glucocorticoids in cancer
- The microbiome in metabolic disease
- Membrane receptors
- Maternal thyroid hormone and child brain development
- Central and Eastern European heritage in the genetics of hypopituitarism
- The immune system in obesity

Debates

Get yourself involved in great discussions on some controversial topics:

- The proper roles of GLP1-agonists and SGLT2 inhibitors in diabetes management
- Vitamin D measurement
- Treatment of subclinical hypothyroidism
- Management of puberty in transgender adolescents
- Adrenal venous sampling before surgery for primary hyperaldosteronism

Meet the experts

Encounter your favourite topic, expert, or both, and dive into:

- Cardiovascular risk reduction in endocrine patients
- Steroid profiling in adrenal disease
- Perioperative management of pituitary patients
- Molecular cross-talk in obesity
- Diagnostic challenges in Cushing's syndrome
- Gynaecomastia: evaluation and management
- Use of calcitonin in diagnostics and follow-up of medullary thyroid cancer and much more...

Symposia

All Focus Areas will be covered, as invited speakers from around the globe present at 30 different symposia. The programme also features special topics, such as novel guidelines, the EYES symposium, and late-breaking news.

Oral communications and posters

The programme gives high priority to the presentation of submitted abstracts, with 14 oral communications sessions and 3 attended poster events. Make sure you submit your abstracts by 3 February 2020 at www.ece2020.org.

Nurse programme

Four sessions for nurses will examine assessment and management of functioning pituitary tumours and gender dysphoria, discuss fertility in men with a nurse expert, and support nurses' professional development.

We thank everyone for their input into the programmes, especially our colleagues on the Programme Organising Committee. Our gut feeling tells us that we have an excellent programme – but don't rely on your guts, use your brains and meet us in Prague!

Attila Balázs Patócs

ECE 2020 Programme Organising Committee Co-Chair (Basic Science)

Jens Otto Lunde Jørgensen

ECE 2020 Programme Organising Committee Co-Chair (Clinical)



Our award lecturers



Annamaria Colao
Geoffrey Harris Award

Love at first sight. I was a young student, with some experience in cardiology, pathology and, briefly, neurosurgery (it was not in my soul). My study of endocrinology began in a group focused on thyroid diseases. However, I fell in love with a charmer: so complex, difficult to interpret, with many qualities and attitudes, still to be entirely discovered... the hypothalamus.

Like all lovers, I decided to dedicate my work to better understanding – of the hypothalamus–pituitary unit. Regulation of the growth hormone/prolactin axis was the topic of my thesis for graduation,

specialisation and PhD. I built a large group of researchers around hypothalamic–pituitary disorders.

Over the past two decades, we identified novel therapeutic strategies in pituitary tumours, far beyond acromegaly and prolactinomas, including Cushing's disease, non-functioning pituitary tumours and craniopharyngiomas. Developing solid research, particularly concerning novel markers, is not trivial, and requires a broad range of experts in an integrated team.

We undoubtedly now know much more about the underlying molecular events but, despite extensive research and significant advances, pituitary tumours still present major challenges for patient management. My dream? To find the clue to treating the most malignant tumours, which still kill our patients today.



Davide Calebiro
European Journal of Endocrinology Award

Over the last 18 years, my research has focused on the basic mechanisms of G protein-coupled receptor (GPCR) signalling and the alterations in endocrine disease. My group develops innovative microscopy methods that allow us to monitor GPCR signalling in living cells with unprecedented spatio-temporal resolution. These methods are so sensitive that they can visualise individual receptors as they interact with their signalling partners.

This has led to several unexpected discoveries, including the fact that GPCRs signal not only at the plasma

membrane but also at intracellular sites, such as early endosomes or the Golgi complex. These findings are profoundly changing our understanding of how GPCRs function, and might pave the way to innovative drugs, capable of selectively modulating GPCRs at specific subcellular sites.

Moreover, with our expertise in GPCR signalling, we have helped clarify the pathogenesis of several endocrine disorders. This includes the discovery that activating mutations in the catalytic subunit of protein kinase A are responsible for adrenal Cushing's syndrome.

While a lot remains to be done, these basic discoveries will hopefully lead to new pharmacological therapies for endocrine and metabolic diseases in the future.



Richard Eastell
Clinical Endocrinology Trust Award

The fractures that result from postmenopausal osteoporosis have a major public health impact. We have several drugs we can use to reduce the risk of these fractures. Most of these are anti-resorptive, such as the bisphosphonates (alendronate, ibandronate, risedronate and zoledronate), raloxifene, oestrogen and denosumab.

Until recently, the only anabolic agent available was teriparatide. However, in the last couple of years, two new agents have been approved in some countries, namely abaloparatide (an analogue of parathyroid

hormone-related protein) and romosozumab (an antibody against sclerostin). Important questions arise, such as should the anabolic drugs be given early in the course of osteoporosis or just in severe disease? What treatment should be given after these anabolic treatments?

The anti-resorptive drugs are very safe. However, it has become common practice to have 'drug holidays' in patients taking bisphosphonates for 3–5 years, to prevent rare side effects, such as atypical femur fracture. Thus, the indications for treatment, the order of treatment and the individualisation of treatment are all important considerations for optimal patient care. We highlighted these issues in recent guidelines from the Endocrine Society, endorsed by ESE.



Olle Kämpe
European Hormone Medal

Autoimmune endocrine diseases, such as type 1 diabetes and autoimmune adrenal insufficiency (Addison's disease), often aggregate in families. Despite being universally lethal before the 20th century, the predisposing genetic variants have remained in the population, probably conferring advantages even at the price of an enhanced risk of developing autoimmunity.

With carefully phenotyped patients and geographically matched controls, strong signals can be obtained in genome-wide association studies (GWAS), even with

small cohorts in rare diseases. In patients with autoimmune adrenal insufficiency who are positive for 21-hydroxylase autoantibodies, genetic variants of MHC, *BACH2* and *AIRE* have emerged as the most important risk genes.

Monogenic disorders, such as autoimmune polyendocrine syndrome (APS-1) and immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), have proved invaluable in understanding the events eventually leading to endocrine autoimmunity. These syndromes have helped us identify the genes *AIRE* and *FOXP3*, critical for important tolerance mechanisms. They also represent good examples of how research on rare disorders translates into novel diagnostic tools and better understanding of more common autoimmune disorders and, at the same time, improve clinical care practices for patients with APS-1 and IPEX.



The Endo Explorer

Embracing a multi-disciplinary approach



The team in Prague (L–R): Michal Kršek, Ivan Raška, Václav Hána, Adéla Krausová, Jan Jiskra, Hana Vítková, Judita Klímová, Tomáš Brutvan and Václav Hána Jr

The Department of Internal Medicine at Prague's University Hospital has focused on endocrinology and metabolism since it was founded in 1945. Václav Hána and Michal Kršek reflect on the huge breadth of its achievements.

Several teams have evolved in the almost 75 years of our department's history. They concentrate on neuroendocrinology, thyroidology, adrenals and secondary hypertension (namely primary hyperaldosteronism and pheochromocytoma), osteology, diabetes mellitus and hyperlipoproteinaemia. The groups co-operate on interdisciplinary topics. Our endocrine research has a clinical orientation, and we have published our results in well-regarded journals.

Neuroendocrinology

Basic science in neuroendocrinology was represented by Vratislav Schreiber, who predicted the existence of thyrotrophin-releasing hormone (TRH) in the early 1960s. His contribution to the discipline was acknowledged in *Pioneers in Neuroendocrinology*.¹

Josef Marek established clinical neuroendocrinology here in the 1970s, and it has since developed with the latest laboratory methods and techniques. We form a multidisciplinary team with other specialists: our neuroradiologists and ophthalmologists, neurosurgeons in the Military Hospital in Prague, and radiosurgery using the Leksell gamma knife (LGK). We provide multimodal therapy to patients with sellar tumours (pituitary adenomas) with a very good prognosis. Acromegalic patients are endocrinologically cured by surgery in 61% of cases. These results are the work of excellent neurosurgeons, supported by the use of intraoperative magnetic resonance imaging.²

A consequence of our 25-year-long co-operation with colleagues on the LGK, and our large cohort of patients with

pituitary neuroendocrine tumours including residual disease who have undergone LGK radiosurgery, was that we could analyse data from these patients over a long follow-up period.

The effect of radiosurgery on the hormonal activity of residual tumours was fastest for Cushing's disease (median 30 months), then acromegaly (median 54 months), and the most resistant were prolactinomas. Nevertheless, the LGK radiosurgery alone or in combination with dopamine agonists normalised prolactin levels in more than 81% of dopamine-agonist resistant patients. Almost all irradiated tumours stopped proliferating and the majority shrank. We also found out that keeping the mean radiation dose to the residuum of the pituitary gland below 15Gy, and the dose to the distal stalk below 17Gy, prevents development of postradiation hypopituitarism.^{3,4,5}

Adrenal incidentalomas

Evaluation of the hormonal activity of adrenal incidentalomas remains a very real problem. In co-operation with Martin Hill, a skilled steroidologist at the Institute of Endocrinology in Prague, we have focused our attention on this area.

Evaluation of the steroid metabolome comprising 83 serum steroids by gas chromatography–tandem mass spectrometry (GC-MS/MS) in patients with unilateral and bilateral adrenal incidentalomas showed changes in steroidogenesis in individuals with subclinical hypercortisolism. The most discriminatory was dehydroepiandrosterone sulfate, followed by midnight serum cortisol, epiandrosterone sulfate, androsterone sulfate and 16 α -hydroxypregnenolone. Subclinical hypercortisolism was associated with decreased levels of adrenal androgens, their metabolites, and pregnenolone metabolite. GC-MS/MS is a powerful tool for measuring serum levels of these undescribed changes in steroid metabolism, which are characteristic of subclinical hypercortisolism in adrenal incidentalomas.⁶



'Interdisciplinary projects provide a useful perspective from which to generate interesting outcomes'

Cushing's syndrome

Using the same method to measure 94 serum steroids, we looked at steroid fingerprints in different subtypes of Cushing's syndrome. Patients with Cushing's disease and ectopic adrenocorticotrophin (ACTH)-producing tumours showed elevated levels of androgens and their metabolites when compared with healthy controls. Mineralocorticoid precursors were also elevated in ectopic ACTH syndrome. The levels of androgens were decreased in adrenal adenomas and bilateral macronodular adrenal hyperplasia (BMAH).

ROC analysis showed 100% sensitivity and 93.6% specificity for 11 β -hydroxyepiandrosterone sulfate in discriminating between Cushing's disease and ectopic ACTH secretion. We didn't find any significant ($P < 0.05$) difference in steroids that would discriminate between BMAH and unilateral adenomas causing Cushing's syndrome. Various causes of Cushing's syndrome show particular steroid fingerprints that can be used for the purpose of discrimination and may help to achieve appropriate clinical diagnoses.⁷

Phaeochromocytoma and paraganglioma

Specialists in hypertension in our department performed studies in a large cohort of 179 patients with pheochromocytoma and paraganglioma. Their novel findings included the observation that patients with reverse dipping of blood pressure have more pronounced target organ damage than other patients, and that the noradrenergic phenotype also has more pronounced target organ damage of the heart and blood vessels.⁸

This group also demonstrated higher concentrations of fibroblast growth factor 21 (FGF21) in patients with pheochromocytoma/functional paraganglioma, and the normalisation of FGF21 after tumour removal.⁹



Thyroid studies

Within a broad field of thyroid research, our department focuses on evaluating thyroid screening in pregnancy, including its cost-effectiveness, the relationship between thyroid dysfunction and gestational diabetes, and thyroid cancer in pregnancy.¹⁰ A national project is being introduced to examine the value of universal thyroid screening in pregnancy, supported by the European Social Fund.

Our thyroidologists also test novel techniques for ultrasound of thyroid nodules, i.e. elastography, and look at the possibility of improving thyroid fine needle aspiration.¹¹

Diabetes and bone

With a focus on glucose monitoring and different modalities of therapy, our diabetologists showed that real-time continuous glucose monitoring was superior to self-monitoring of blood glucose (SMBG) in reducing glycated haemoglobin and hypoglycaemia and achieving other desired end-points in individuals with type 1 diabetes, regardless of their insulin delivery method. Real-time continuous glucose monitoring+multiple daily injections (MDI) can be considered an equivalent, but lower cost, alternative to sensor-augmented insulin pump therapy, and superior to treatment with SMBG+MDI or SMBG+continuous subcutaneous insulin infusion therapy.¹²

Bone fragility, particularly in type 2 diabetes, may contribute to fracture risk, independent of bone mineral density. Our research topics in osteology include the utility of biochemical markers of bone and glucose metabolism, soluble receptor for advanced glycation end products (sRAGE) and its gene polymorphisms in assessing diabetic bone fragility.¹³ Our osteologists are beginning a longitudinal project to evaluate whether the maintenance of muscle mass, especially in the lower extremities, and/or reduction of central fat mass can prevent fractures.¹⁴

We believe that, in the field of endocrinology, interdisciplinary projects provide a useful perspective from which to generate interesting outcomes.

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Endocrine work-up in obesity



A new ESE Clinical Practice Guideline on the endocrine work-up in cases of obesity has recently been published in *European Journal of Endocrinology*.¹ Here, Renato Pasquali, who led the working group behind its development, reflects on its importance and role in clinical practice.

Obesity is a rapidly emerging condition worldwide and is associated with a series of diseases, including, but not limited to, metabolic syndrome, type 2 diabetes, hypertension and infertility.

The endocrinology of obesity

The 2015 European guidelines² acknowledged the increased prevalence of many endocrine conditions in obesity. Interest in the endocrinology of obesity is supported by the fact that the condition is frequently associated with numerous hormonal alterations, which must be identified in order to activate an adequate therapeutic plan. On the other hand, it should be noted that several endocrine disorders may be associated with obesity and, in most patients, weight loss by appropriate intervention, based on individual needs, may also improve related hormonal imbalance. Most of these hormonal alterations are secondary to the development of obesity.

It is quite common for endocrinologists not to deal with obesity and its associated endocrine and metabolic alterations. At the same time, most clinicians who are dedicated to the diagnosis and treatment of obesity do not take much notice of alterations in the various endocrine systems and in the concentrations of hormones in obese patients.

In recent decades, several guidelines have been proposed by the European Society for the Study of Obesity (EASO). However, the impact of an altered hormonal system on the development of obesity and, conversely, that of obesity on the hormonal system have been underestimated.

A place for new guidance

The new ESE guideline focuses on the fact that a substantial number of hormonal changes are involved in an increased disease burden. The concomitant hormonal disorders that may be present should be properly diagnosed. In addition, detection of a number of hormonal alterations (dependent on age and sex) can, in turn, make the assessment of hormonal changes complicated and misleading.

It is the aim of this ESE guideline to concentrate on the endocrine work-up in patients with obesity and on the potential therapeutic consequences of hormonal alterations associated with obesity.

A broad hormonal spectrum

Hormonal alterations associated with obesity are multiple and may partly differ according to sex. They include changes in thyroid hormones, glucocorticoids, androgens and oestrogens, neuroendocrine hormones, central and peripheral peptides, adrenocorticotrophin, luteinising hormone, follicle-stimulating hormone, prolactin, growth hormone, aldosterone, insulin, etc.

Examples of endocrine diseases causing or contributing to obesity include hypothyroidism, androgen deficiency in males or an excess in women, Cushing's disease or syndrome, hypopituitarism, hypothalamic lesions, growth hormone deficiency, ovarian failure, leptin deficiency, and more besides.

In clinical practice, diagnostic and treatment decisions should take into account the recommendations, and also the clinical judgement of the treating physician.

The role of the endocrinologist

In most cases, despite obesity being a condition of endocrine and metabolic imbalance, obesity is not caused by other endocrine diseases or hormonal disturbances. Furthermore, the prevalence of overweight and obesity is such that standard referral to an endocrinologist would not be compatible with the available resources in most countries.



Guideline Working Group members (L-R): Severine Ledoux, Ferruccio Santini, Javier Salvador, Olaf Dekkers, Renato Pasquali, Hermann Toplak, Mariana Monteiro, Felipe Casanueva, Leonie van Hulsteijn and Martin Haluzik



'The impact of an altered hormonal system on the development of obesity and, conversely, that of obesity on the hormonal system have been underestimated'

As one might anticipate, endocrinologists should be consulted in the case of clear suspicion of an endocrine disease in both men and women. In addition, as hormonal alterations may be related to obesity itself, and because the clinical signs and symptoms of endocrine conditions can be difficult to distinguish from obesity, the ESE guideline firmly supports the idea that referral to an endocrinologist should always be considered for patients with morbid obesity. Further reasons for referral to an endocrinologist may include therapy-resistant obesity and/or rapid weight gain and, in any case, candidates for bariatric surgery.

Common hormonal disorders which should be considered include: altered thyroid hormone concentrations, decreased androgens in obese men with dysmetabolic hypogonadotropic hypogonadism, increased androgens (particularly in adolescent and young women), altered cortisol in chronically stressed individuals, and hypertension (particularly in patients with therapy-resistant hypertension).

In conclusion, the team responsible for the ESE guideline believes that the recommendations may be useful for many endocrinologists, who can be of considerable help, not only in the diagnostic process, but also in the treatment of endocrine disorders related to obesity.

Ultimately, if endocrinologists are able to focus greater attention on the hormonal disorders associated with obesity, this could provide an excellent driving force for the treatment of obesity at every stage of life, both in men and in women.

Renato Pasquali

on behalf of the Guideline Working Group

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2. Yumuk et al. 2015 *Obesity Facts* **8** 402–424 with erratum at **9** 64.

Endocrine Connections Editor-in-Chief opportunity

The European Society of Endocrinology and the Society for Endocrinology are seeking a new Editor-in-Chief for *Endocrine Connections*.

Endocrine Connections is an open-access journal, publishing basic, translational and clinical research and reviews in all areas of endocrinology.



This is an exciting opportunity to steer the direction of a fast-growing society journal over a period of 5 years. The role includes:

- identifying new topic areas to attract content
- structuring the international editorial board
- overseeing the peer review process
- working with the publisher to ensure the journal remains in line with the societies' visions.

Starting in January 2021, this position has a 5-year term and attracts an honorarium. Applications will be accepted until 1 April 2020. For more details of the role, including how to apply, visit www.bioscientifica.com/about-us/current-vacancies/editor-in-chief-for-endocrine-connections.

Endocrine-Related Cancer Editor-in-Chief opportunity

The Society for Endocrinology is seeking a new Editor-in-Chief for its high-impact journal *Endocrine-Related Cancer*.



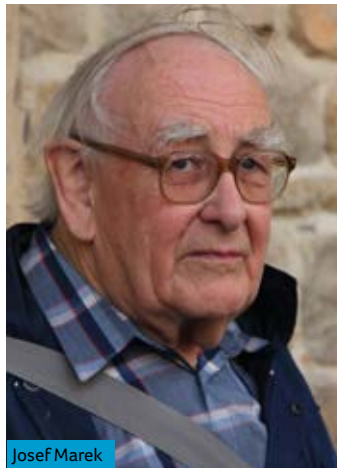
Endocrine-Related Cancer publishes basic laboratory, translational and clinical investigations of human health and disease, focusing on endocrine neoplasias and hormone-dependent cancer. Its current impact factor is 4.774.

Starting in January 2021, the holder of this position will oversee the peer review process and play a key role in the strategic development of the journal. The Editor-in-Chief triages all submitted manuscripts and identifies new and emerging topics, with the aid of the publisher and the editorial board.

Applications for this role should be submitted before 1 April 2020. Full details are available at www.bioscientifica.com/about-us/current-vacancies/editor-in-chief-for-endocrine-related-cancer.



A history of endocrinology in the Czech Republic



Josef Marek

'I am happy that our experience with gamma knife radiosurgery has improved the care of patients with pituitary adenoma.'

It was with great sadness that we learnt of the death of Professor Josef Marek in late October 2019. Professor Marek was a truly outstanding, internationally respected, endocrinologist. His loss is sorely felt, particularly in his homeland of the Czech Republic. We are honoured that the last article he wrote was this history, for *ESE News*. We extend our condolences to all who knew him.

The Czech Society of Endocrinology was founded on 1 January 1938. It was presided over by Professor Josef Charvát, a famous endocrinologist, renowned all over Europe.

The activity of the Society was very limited during World War II (1939–1945). It was renewed after the war at two sites in Prague. Professor Charvát became the Head of the 3rd Department of Internal Medicine at the 1st Faculty of Medicine of Charles University. Another prominent Czech endocrinologist, Professor Karel Šilink, practised mostly in the state Institute of Endocrinology, which was founded in 1957. In the 1940s, he started to introduce iodination of edible salt as a means of preventing thyroid disorders due to iodine deficiency. The Czech Republic was only the second state in Europe (after Switzerland) to do this.

The 3rd Department of Internal Medicine, led by Professor Charvát, was a great clinical centre, covering all aspects of endocrinology. Clinical care and research were performed by specialists. When I entered the Department in 1965, there was nobody to focus on the pituitary, and I happened to favour it.

At that time, it was difficult to treat diabetes insipidus, because all the drugs at our disposal were practically ineffective. Shortly afterwards, Professor Milan Zaoral discovered and synthesised the drug called desmopressin (D-arginine vasopressin). Desmopressin has now been in clinical use for many decades all over the world. My first task at the Department was to organise clinical testing in patients with diabetes insipidus.

Professor Vratislav Schreiber was another great experimental endocrinologist, who was known

worldwide, and featured in the monograph *Pioneers in Neuroendocrinology*.¹ He also worked in the 3rd Department of Internal Medicine, and studied the relationship between the hypothalamus and the pituitary. He was the first to discover the existence of thyrotrophin-releasing hormone and its function.

During the first 20–30 years after World War II, the possible methods for measuring hormones were limited. The radioimmunoassay technique had not yet been developed. Due to the political situation at the time, the exchange of knowledge with those in Western Europe and America was restricted, and travel to those places was even more so. By chance, I had the opportunity to go to France for a short time and study the biological method (using the chick embryo) for dosage of somatomedins (IGF-1), which provided information about the quantity of growth hormone present.

Later on, when precise diagnostics were available, the problem of treatment still remained. Our department focused on the treatment of pituitary disorders, especially pituitary adenomas. Despite advancements in neurosurgery, the complete removal of pathological tissue is not successful in all cases. In such unsuccessful cases, other treatments (such as medical therapy and radiotherapy) are indicated.

I was happy to lead the collaboration between our institution and the Department of Stereotactic and Radiation Neurosurgery at Na Homolce Hospital in Prague, which resulted in treatment of pituitary adenoma by gamma knife radiosurgery. I was eager to learn

what results radiosurgery would produce. We proved that gamma knife radiosurgery is efficient, and that the success of this treatment depends on the type of pituitary adenoma.

The most common side effect was the development of hypopituitarism, and so we studied the factors which can produce this unfavourable result. It was proved that the two most important factors in the development of hypopituitarism were the dose to the pituitary gland and the dose to the distal infundibulum. Hypopituitarism can be limited if the safe mean dose to the pituitary of <15Gy and the maximal dose to the distal infundibulum of <17Gy are maintained.

I am happy that our experience with gamma knife radiosurgery has improved the care of patients with pituitary adenoma.

Josef Marek

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A day in the life of...

...a diabetologist/endocrinologist in the Czech Republic



05.20

Before the alarm goes off, my 'internal clock' somehow wakes me up and I stumble to the bathroom. After quickly washing my face, I convince myself to do my regular morning exercise (as I always suggest to my patients). Finally, it's over and I can have a quick shower and a well-deserved breakfast.

06.55

I am at work with my first cup of coffee, looking through emails and my diary. The day does not look that good: a grand round, an outpatient clinic and a long to do list, with several leftovers from previous days.

08.00

We have a morning department meeting, with a report on the patients who have been admitted.

08.30

Back in my office, I finish a presentation for medical students and answer some more emails. It seems an ineffective exercise, as almost every answered email creates some further response. Then I get a phone call from our study nurse, who reminds me to see two patients participating in a clinical trial.

10.00

The grand round generated a lot of interesting discussions. Our ward is full of quite complex patients, primarily with type 1 diabetes before or after kidney and pancreas transplantation, some type 2 diabetes patients with a diabetic foot requiring inpatient treatment, and a couple of endocrine patients (one being my patient with adrenal incidentaloma, awaiting a decision on whether he can go to bariatric surgery).

11.30

Luckily the grand round was quick and effective today, and I get back to my computer. I ignore the emails this time, and try to do my duties as co-Editor-in-Chief of *Journal of Endocrinology*/*Journal of Molecular Endocrinology*.

While triaging the manuscripts to decide which should go for a full review, I answer a few phone calls – most are from patients interested in obtaining a novel diabetes treatment that we discussed on TV several weeks ago. Almost everybody seems interested in participating in the trial and wants to chat with me on this topic.

12.00

I meet briefly with colleagues from my lab. We talk about the upcoming deadline for the grant applications and the papers to be written. There is no doubt that we have a bright future ahead. We just need the good reviewers to appreciate our brilliant ideas!

12.30

It's time for a quick lunch and pleasant chat with colleagues. It would be nice to have some coffee and desert as well. I have just read the paper claiming that coffee has a positive influence on gut microbiota. Nevertheless, the microbes have to wait: my outpatient clinic is due and some patients are already eagerly expecting me.

13.00

The outpatient clinic does not go that well. As the traffic in Prague is even worse than usual, some patients arrive late, and two arrive unannounced, claiming they had an appointment. At 16.45, I simply have to take a 10-minute break, after a particularly long discussion with poorly controlled patient with type 2 diabetes patient. They did, however, bring me some excellent milk chocolate. I eat half of it along with a cup of coffee. Almost immediately, the world seems a much better place, and my understanding regarding patients' dietary non-compliance increases markedly.

17.30

At the end of the clinic I return to my office. I just got an email from *ESE News* to say my 'Day in the life of a Czech endocrinologist' was due 3 days ago, a reminder from *Journal of Clinical Endocrinology & Metabolism* that my review was due 2 days ago, and three emails from patients asking for an appointment. Luckily, I still have the rest of the chocolate with me...

19.00

I finish apologising for all the late responses to emails and try to work on the review on the endocrine function of gut. While writing about the stimulating effect of food on glucagon-like peptide-1 secretion, I get so hungry that I have to stop, have a quick bite and go home. It indeed appears to be true that the brain can burn half one's daily carbohydrates, at least in my case...

20.15

I am finally home with my family. My son, my wife and my daughter are not that excited about my return as they are watching a Champions League football match – Slavia Praha is playing Barcelona. All my noble plans to work on the review paper just disappear and I watch the game with them.

22.15

Oh no! We lost 1:2, despite being better and having three goal chances in the last 10 minutes. I hate Lionel Messi! And I should have worked on my review instead, but it is too late now.

23.00

I am in bed trying to read but, after 10 minutes, I just fall asleep. I have a dream about a vacation in the beautiful Czech Krkonoše mountains and sleep soundly – until 05.20.

Martin Haluzík

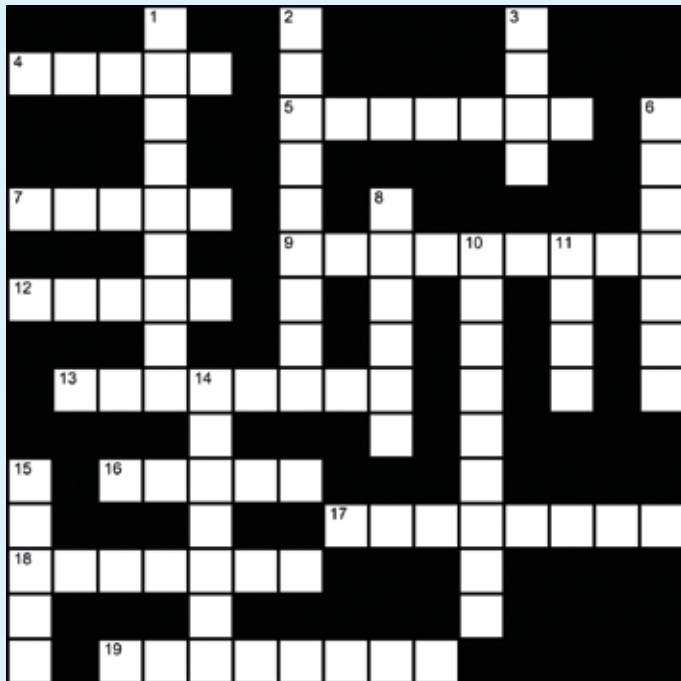
Deputy Head, Diabetes Centre, Centre for Clinical and Experimental Medicine, Prague, Czech Republic



The Endo Crossword



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.



Across

- 4 and 8 down** First Director of Prague's Institute of Endocrinology (5,6)
5 A syndrome of excessive ACTH secretion (7)
7 Enzyme regulating blood pressure (5)
9 Plum brandy, speciality of **14 down** (9)
12 and 18 across 20th century endocrinologist who led the Czech Scout Association (5,7)
13 Hormone stimulating T cell development (8)
16 and 15 down Endocrinologist, Czech Radio's 2016 'Most Respected Czech Abroad' (5,5)
17 Hormone regulating levels of **11 down** (8)
18 See **12 across**
19 See **10 down**

Down

- 1** Intestinal hormone inhibiting food intake (7,2)
2 Patron saint of **6 down** (9)
3 Czech Republic's second largest city (4)
6 Region forming the western Czech Republic (7)
8 See **4 across**
10 and 19 across Famous Czech cheese (9,8)
11 Mineral typically held in a porphyrin ring (4)
14 Region forming the eastern Czech Republic (7)
15 See **16 across**

Solution

Answers to the puzzle in issue 40

Across

1. Phe, 4. TTC, 6. Magnesium, 7. Glucokinase, 9. Melanocortins, 11. TTT, 13. Inhibin, 14. Inulin, 15. Ecdysone

Down

1. POMC, 2. Eyes, 3. Leukonychia, 4. Thyroxine, 5. Glicentin, 8. Calcitriol, 10. Iodine, 12. Blue

Save the date

For more information see www.eese-hormones.org.

26th ESE Postgraduate Training Course on Endocrinology, Diabetes and Metabolism

19–22 March 2020

Tbilisi, Georgia

ECE2020

22nd European Congress of Endocrinology

23–26 May 2020

Prague, Czech Republic

European Board Exam

10 June 2020

Various locations

23rd European Congress of Endocrinology

22–25 May 2021

Stockholm, Sweden

Deadlines

3 February 2020

ECE 2020

Abstract submission

19 February–18 March 2020

European Board Exam

Registration open

28 February 2020

ESE Awards 2021:

- Geoffrey Harris Award
- *European Journal of Endocrinology* Award
- Clinical Endocrinology Trust Award
- European Hormone Medal
- Jens Sandahl Christiansen Award

Nomination deadline

1 March 2020

Small Meeting Grants

Application deadline

8 April 2020

ECE 2020

Early bird registration deadline

Did you know?



Ancient genes tackle modern pollutants

Human exposure to certain pollutants has only arisen recently in our evolution. But our distant ancestors' adaptation to novel toxins may give some of us a genetic advantage in the face of new threats.

Trumble & Finch contemplated six phases in evolution where human exposomes (lifelong environmental exposures) changed significantly: the initiation of increased mobility, the introduction of fire, the domestication of animals, the development of dense communities and, later, industrialisation, with the final phase being our adaptation to current and future challenges.

Genetic adaptations during this 6-million-year period were analysed alongside the occurrence of novel toxins. Adaptation to some ancient toxins may persist in genetic variations associated with inflammation and longevity. Some genes (such as *ApoE4*) may now be deleterious, having conveyed an advantage in earlier times, as our environment has changed faster than our genetics.

See *The Quarterly Review of Biology* 2019 **94** 333–394.