

Issue 45 Summer 2021

ESE News

The newsletter of the European Society of Endocrinology

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A detailed 3D molecular model of a protein, likely an antibody or a hormone receptor, rendered in blue and teal. The structure is complex, showing multiple alpha-helices and beta-sheets. The background is a light green with a faint, repeating pattern of the same protein structure.

Where endocrinology meets immunity

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Why EDCs are an issue for us all
COVID-19 and its endocrine complications



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Editorial



Immunity: we, as well as patients, politicians and the general public, have probably heard more about this single area of medical research than any other since March 2020. It has been both refreshing and distressing to see scientists' profile raised to such an extent in the news media during the pandemic.

Against this background, endocrinologists need to understand how immune responses – whether to SARS-CoV-2 or to anything else – relate to our own discipline, our own research and our own practice. For instance, how is our understanding of autoimmune endocrine disease developing? How will patients with endocrine disease respond to COVID-19? What reassurance can we offer endocrine patients about vaccination? What endocrine symptoms might COVID patients exhibit?

In this issue, we have sought the latest updates from researchers working in immunology, in endocrinology and at the interface between the two. On page 8, Alojz Ihan gives an immunologist's view of the future course of the COVID-19 pandemic, and emphasises the importance of building confidence in vaccination amongst all patients. His opinion supports ESE's statement on COVID vaccination, which you will find on page 9.

The prevalence of autoimmune disease has increased. On page 10, Sari Mäkimattila examines the latest theories and evidence behind this observation. Eystein Husebye continues the theme of autoimmune endocrine disease on page 11, relating the results of the first genome-wide association study to identify genetic associations in autoimmune Addison's disease.

Sandro La Vignera and colleagues have analysed the endocrine impact of SARS-CoV-2 on patients without pre-existing endocrine disease. On page 12, they draw analogies with the effects of other coronaviruses and consider potential mechanisms in what is a rapidly growing area of research.

A recent paper by Irene Campi and her group in *European Journal of Endocrinology* studied thyroid function tests in patients hospitalised for COVID-19. She discusses the effects of virus-associated cytokine release on page 14. EuRRECa (the European Registries for Rare Endocrine Conditions) has been collating data on endocrine patients who contracted COVID-19. Turn to page 15 to find out more.

In addition, we present our first opinion article, on page 7. Josef Köhrle (ESE Focus Area Lead on Environmental Endocrinology) reminds us of the responsibility we all have to protect ourselves and our fellow creatures from endocrine disruptors. Josef encourages us all to act without delay in lobbying EU bodies to take action.

This issue of *ESE News* also includes some important welcomes. The first is to ESE's new President: meet Martin Reincke and hear his plans on page 5. The second is to Adrian Clark, the new Editor-in-Chief of *Endocrine Connections*. Adrian shares his thoughts on the future of publishing on page 13. I add my own welcome to the new members of the *ESE News* Editorial Board: Karim Meeran, Walter Vena and Maria Chiara Zatelli. They join us as we enact exciting new plans for your newsletter. Read more on page 3.

Justo P Castaño
Editor, *ESE News*

Cover image: Quaternary protein structure of an immunoglobulin.
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Contributing to a healthier Europe

ESE's new White Paper has been widely welcomed by key figures at the European institutions as a valuable contribution towards improving public health.

Entitled 'Hormones in European Health Policies – How Endocrinologists can Contribute to a Healthier Europe', it provides a European policy focus around obesity, rare endocrine diseases, endocrine cancer and endocrine disruptors.

Its launch by webinar on 4 May was supported by the attendance of key officials, including John F Ryan, Director of Public Health at the European Commission, and several Members of the European Parliament.

Stella Kiryakides, EU Commissioner for Health and Food Safety, warmly

welcomed the White Paper when she spoke at e-ECE 2021, describing it as 'valuable' and adding 'I look forward to working closely with you, to build a healthier European Union.' She stressed the importance of endocrinology for EU Health Policies and invited further collaboration between the EU Commission and ESE.

The White Paper is endorsed by 45 national endocrine societies and seven European and international specialist societies, and is the product of a 2-year consultative process.

See highlights from the launch, including comments from John F Ryan and European politicians, and subscribe to the ESE YouTube channel at www.youtube.com/watch?v=9Q5bo7jrTx4.

You can download the White Paper at www.ese-hormones.org/publications/policy-white-paper.



ESE News is evolving

You may notice some differences in this issue of *ESE News*. Over the next 2–3 years, the Editorial Board, led by our visionary Editor Justo Castaño, is applying a programme of content and format development, to ensure that we continue to provide you with the information you need, in ways that you find easy to access.

We have started by moving towards more opinion-driven content, to bring you the latest expert views and stimulate healthy debate. You can look forward to discussions on topics across endocrinology and at the interface with other disciplines. We will address developing areas, where answers are not always certain. We will continue to expand upon the latest clinically relevant content, to keep you up to date with best practice. We will invite experts from related disciplines to share their perspectives. We will give you an insight into your Society's plans, and seek your opinions.

The content will be more aligned with the ESE Focus Areas, and Focus Area Leads will join the Editorial Board as guests, to advise on topics to cover. Icons alongside articles will reflect the relevant

Focus Areas and other categories. Those below are used in this issue.

The future will see development of interactivity, alongside the familiar print version. We will provide a digital version that is more integrated with other sources of information and social media.

This change is an evolution, not a revolution. It is taking place over the course of several issues, and we will maintain our ethos of serving ESE members and listening to your views. Part of the process will see a change in name, to reflect a shift from principally being a newsletter to becoming a vehicle for an exchange of ideas and proactive engagement with ESE's activities. Watch this space to find out more!

In the meantime, if you would like to share your thoughts on how *ESE News* should develop, please contact us on info@euro-endo.org.

New ESE Research Funding Hub

ESE members will benefit from a new European Research Funding Hub on the ESE website.

This Funding Hub will provide up-to-date information on research funding schemes launched by the European Commission. Between now and 2027, a total healthcare research budget of €13.2 billion will be available (€8.1 billion from Horizon Europe and €5.1 billion from the EU4Health programme).

To support researchers, a Hub feature entitled 'Your Funding Journey' will make it easier to find opportunities in line with their profile. The Hub will also detail when research calls are due to be published by the European Commission.

The site explains how ESE can be a supportive partner for those applying for funding from EU Research schemes.

This funding is intended to address the inequalities in financial support across Europe. There has been a relative lack of awareness of these programmes (as demonstrated by the findings of ESE's 2018–2019 survey Mapping Endocrinology in Europe). The ESE Science Committee, headed by former Chair Felix Beuschlein, took the initiative to develop this resource to support ESE members.

All researchers, not just those early in their careers, but also those who are more advanced, should visit www.ese-hormones.org/research/european-research-funding.



 **Adrenal and Cardiovascular Endocrinology**

 **Environmental Endocrinology**

 **COVID-19**

 **Publications**

 **Diabetes, Obesity, Metabolism and Nutrition**

 **Thyroid**



Membership to meet your needs!

The ESE Membership Committee has recently reviewed all aspects of ESE's membership offering, to ensure it meets the evolving needs of all members – now and in the future. The redeveloped categories will better serve all individual members and reflect our community's diversity.

All members will be placed in one of five new membership groups, at the relevant career stage (see below).

What does this mean for you?

We will be better able to tailor activities to your needs and to provide you with the most

relevant member benefits and communications. There will be no change to membership fees for 2022 (renewal from October 2021 for the 2022 calendar year).

What happens next?

In late July, you will be sent an email with details of your new membership category for you to check. If it is correct you don't need to do anything, BUT if we have allocated you to the wrong group (e.g. you are no longer eligible for early career membership) you can easily let us know through a reply link in the email.

Your 2022 renewal will then be for the new membership category – and we will highlight the benefits and activities that we think will interest you throughout the year.

We are excited about these positive developments which will help ESE to remain your supportive partner throughout your career.

Anton Luger and Jérôme Bertherat
ESE Membership Committee Co-Chairs

Martin Reincke
ESE President

Congratulations

Two of the five recipients of the Endocrine Society's 2021 Early Investigators Awards are members of ESE.

We congratulate Ana Aulinas and Manuel D Gahete, as well as the other award recipients. Both Ana and Manuel are from Spain and each has previously received a Young Investigator Award from ESE.

Ana's recent work has focused on oxytocin deficiency in patients with hypopituitarism, and Manuel's has been on crosstalk between neuroendocrine systems and pathologies such as endocrine-related cancers and metabolic diseases.

You can read more about them at www.endocrine.org/awards/early-investigators-awards/2021-early-investigators-award-winners.

New ESE membership groups

Clinician	Clinician Scientist	Scientist	Nurse	Allied Health Professional
Full	Full	Full	Full	Full
Early Career	Early Career	Early Career	Early Career	Early Career
Student	Student	Student	Student	Student
Retired	Retired	Retired	Retired	Retired

From the ESE Office

I'm writing this hot on the heels of a successful virtual e-ECE 2021. I was delighted to see the success of our new features. These included the interactive networking tools, the extended Meet the Expert sessions, which allowed you to discuss very diverse topics with clinical experts, and the Spotlight sessions, which comprised live interviews with prominent endocrinologists.

Currently, the ESE Executive Committee is focused on revision of the Society's strategy, which runs until the end of 2021 and therefore needs extending to include our future goals. I am delighted to see that many of the objectives from the existing 5-year plan have been achieved (see panel). These included, for example, our aspiration to reach 5000 members by 2021: we recorded 5009 at the AGM during

e-ECE 2021! We have stayed true to our vision to shape the future of endocrinology, to improve science, knowledge and health.

So much has changed since the strategy was developed, it is truly ready for a refresh. We aim to revise our strategy by the end of the year and will keep you updated on progress.

Another area under consideration is how best to prepare for the post-COVID world. How can we make the most of the opportunities that the pandemic has presented, to reach our audiences for educational purposes in a cost-effective and accessible way? One example is by preparation of a set of online Clinical Update meetings for 2022 to cover an expanded range of topics. We will continue to deliver much of our postgraduate education online.

Notwithstanding these initiatives, we are very pleased to be planning EuroPit 2021: our first



face-to-face meeting since the Europe start of the pandemic. It will take place on 22–24 November 2021 at Les Pensières in Annecy, France.

Finally, I would like to thank our departing Executive Committee members, in particular Andrea Giustina, for his wise and supportive leadership. We welcome Martin Reincke as our new President; you can 'meet' Martin yourself in our interview on page 5.

Although it still seems quite a long way in the future, plans are already underway for ECE 2022 in Milan, Italy. I, like everyone else in the ESE Team, cannot wait to see you all there!

Helen Gregson
Chief Executive Officer, ESE
helen.gregson@ese-hormones.org

Key aims from ESE's current 5-year plan

- To be at the centre of the endocrine community in Europe, acknowledged as the reference point for endocrine science, knowledge and health
- To provide top quality, continuous, endocrine-related education and training for all career stages in clinical practice and basic research
- To foster early career basic and clinical endocrinologists, creating a dynamic community which will inspire them to become endocrinologists and remain in the sector
- To continue to run the leading European endocrine congress, ensuring it is kept current, attractive across the Focus Areas, and viewed as the 'must attend' event for all endocrinologists in Europe
- To ensure that ESE is financially sustainable through excellent management of commercial partnerships and a clear business development strategy



Meet your new President

We welcome Martin Reincke as the new President of ESE. His term began at the AGM during e-ECE 2021 in May. Here, we take the opportunity to ask him a few questions, to get to know him better.

How did you become interested in endocrinology?

This is an unusual story. When I started as a junior doctor on a general internal medicine ward in Cologne University Hospital, I accidentally met Bruno Allolio. Bruno later became a renowned professor and teacher, but died much too early in 2015. He was a senior resident at the same hospital, and he was – an endocrinologist! Bruno was so unbelievably inspiring, enthusiastic and open-minded, I asked him immediately whether he would be my mentor. Without question – I wanted to become an endocrinologist myself. So I had found a life-long mentor and friend, and my field of specialisation. It was a coincidence, but a very lucky one. If Bruno had been an oncologist, I would probably be an oncologist today.

What inspires you, and why?

My very spontaneous answer of today, writing this just after returning from a gorgeous skiing trip in the Engadin Alps in Switzerland, is a non-scientific one. We had great weather and toured through the most impressive mountain scenery, with winter still on the peaks, and beautiful spring in the valleys. This experience of eternity, which nature gives us in rare moments when heaven and earth are in flow, can be most inspiring.

What would you have done if not medicine?

I have a deep affection for philosophy, art and music. This I owe to my parents, who raised me and my three siblings in a humanistic tradition. Therefore, a realistic option would have been to study humanities with a focus on classical philosophy. However, we also had to learn to play instruments, so I might

have followed my younger brother who became a professional viola player. Today, I frequently play violin in various chamber music groups, from Bach to Shostakovich.

What areas of endocrinology most interest you?

My research focuses on the pituitary and the adrenal gland. I have, so to say, adopted two diseases, Cushing's syndrome and primary aldosteronism, like children. My own research is mostly dedicated to improving the diagnosis and treatment of both devastating, deadly conditions. In this context, the €2.5million European Research Council Advanced Grant, which I was lucky enough to be awarded in 2017, has been a great help in identifying disease mechanisms and finding innovative treatments. Still, there is much to do!

Where are we most likely to find you on a day off?

Sitting in the bright sunshine in the garden, extensively reading the newspaper *Süddeutsche Zeitung* and drinking a Darjeeling tea.

What are endocrinology's greatest challenges?

Fighting obesity effectively, beating endocrine cancers, understanding and avoiding the adverse long term health consequences of endocrine-disrupting chemicals, finding treatments for rare endocrine diseases and, finally, anticipating and preventing the dramatic consequences of global warming for our endocrine health.

How can ESE best support its members?

ESE is still a rather young scientific society, founded in 2006. But it has grown to adulthood in less than 15 years, into its current format. Today,

ESE has a broad spectrum of remit, ranging from delivering the best endocrine education for scientists, clinicians, nurses and other healthcare professionals, organising congresses of the highest scientific quality, increasing awareness of endocrine topics through policy and advocacy, and supporting endocrine research and publishing top science in its own journals.

Our Past President Andrea Giustina has done a wonderful job through his 'inclusion plan' to reach out to every stakeholder in the endocrine community: clinicians, scientists, affiliated and associated societies and industry partners, among others. A centrepiece was the intensified collaboration with the national endocrine societies though ECAS (the ESE Council of Affiliated Societies). Strong national societies will make ESE strong, and the other way around. Together, we can give our individual members the necessary network for their daily professional lives and careers. As President, I am proud to serve!

What are your priorities as President of ESE?

The current pandemic is an unforeseen stress test for ESE: are we fit for the future? After just over a year in lockdown with all its terrible consequences, we can say 'Yes, ESE has done much better than expected.' Despite all the shortcomings, the Society has been growing in membership and has achieved most, if not all, of the goals of its 5-year plan.

Nevertheless, we also know that many more challenges are ahead of us, and that we can do even better in some areas. Therefore, my presidency will be dedicated to 'innovation'. How can we optimise virtual meetings? How can we



use the digital environment to deliver customised knowledge and expertise to our members? How can we better support our early career members during the pandemic? What are the next generation of learning tools? How can we benefit the committees? The best way to predict the future is to generate it – by innovation.

What will the pandemic's legacy be?

No question, the pandemic will dominate our life in the near future, and it needs no fantasy to predict that we will have to live with some restrictions. On the other hand, the development of effective and safe vaccinations against COVID-19 is a miracle and one of the greatest success stories of recent decades.

As an optimist, I expect activities to return mostly to normal at the end of my presidency. However, on a more general scale, we have collectively lost our naïve belief in a bright and stable future. We have to face it, our world has become more fragile. With respect to ESE: let's be prepared for the next stress tests, and anticipate future challenges, which we then must overcome through innovation.

What are your words of advice for early career endocrinologists?

Find the right mentor, and love what you are doing – every day!

And for all the members of ESE?

Looking forward to meeting you in person, sooner rather than later. Let's have a cup of coffee together!

'My presidency will be dedicated to 'innovation'. How can we optimise virtual meetings? How can we deliver customised knowledge and expertise to our members? How can we better support our early career members during the pandemic? What are the next generation of learning tools? The best way to predict the future is to generate it – by innovation'



Excitement and engagement: e-ECE 2021

Following ECE 2020's reinvention as a virtual meeting, our wish was to meet face-to-face for ECE 2021 in Prague, the venue intended for the 2020 Congress. As we all now know, SARS-CoV-2 did not give way, and so e-ECE 2021 was born.

Strengthened and encouraged by the experience of e-ECE 2020, we worked hard to conceive the 'perfect' virtual Congress, resembling a live meeting as far as possible and seeking to satisfy participants' expectations.

Six channels allowed attendees to follow all the sessions organised by ESE Focus Area. As well as the opening and closing ceremonies and the prestigious award lectures (see *ESE News* 44, pages 8–9), delegates enjoyed 7 plenary lectures, 27 symposia, 6 debates, 19 clinical and basic Meet the Expert sessions, 15 oral communication sessions, 15 sessions of presented e-Posters, 2 Nurses' sessions and sessions for the European Young Endocrinologists and Scientists (EYES).

Importantly, 8 joint sessions with international associations provided amazing lectures from outstanding basic and clinical representatives. The ESE Council of Affiliated Societies (ECAS) session covered 'Hormones in European health policies', and there were also industry symposia and hub sessions, as well as patient group hub sessions. Early morning yoga sessions gave delegates the chance to get energised at the start of the day!

As always, our goal was to maintain both basic and clinical science at the highest levels and to involve all participants in discussions and interactions

with faculty members. These exchanges were possible with all the speakers, including our plenary presenters, and further reinforced through Meet the Expert extended networking sessions.

Amongst the basic science lectures, Matthias Tschöp (Germany) talked on novel therapeutic approaches to obesity and diabetes. His talk included strategies involving peptide-based multi-agonists targeting multiple hormonal systems for the treatment of metabolic diseases. Some of these revolutionary compounds are in phase 2 and 3 clinical trials and may soon see clinical practice.

The lecture by Eve Van Cauter (USA) was similarly impressive, illustrating the relevance of chronobiology mechanisms in the function of endocrine organs and the critical role of circadian clocks in appropriate metabolic responses.

Also noteworthy was the symposium on the brain sequelae of COVID-19. Vincent Prevot and Olivier Collange (France) provided basic and clinical perspectives (respectively) on the role of the hypothalamus as a hub for SARS-CoV-2, and on the impact of the infection on neurological function.

From a clinical viewpoint, the oral communications provided ground-breaking news, including the presentation by Peter Schwarz (Denmark) on 26 weeks



of treatment with a long-acting parathyroid hormone analogue. This may become a new treatment regime for hypoparathyroidism, as it enables stable calcium homeostasis and improved quality of life. Several symposia provided new knowledge on important topics such as adrenal incidentalomas and approaches to intermediate thyroid cancers. Meet the Expert sessions allowed for in-depth discussions of timely topics, including long term effects of testosterone replacement therapy.

This was an exceptional Congress in terms of the basic and clinical science brought to the attendees and, importantly, its virtual nature meant we could reach colleagues around the globe. Its great success was thanks to the contributions of the Programme Organising Committee (POC), ESE President and President-Elect and other Executive Committee members,

along with the valuable and tireless support of the ESE staff, including the efficient technical assistance of the Event Manager.

Despite holding such a successful Congress, we really hope to see you all in person in Milan, Italy, at ECE 2022. This will give us the opportunity to enjoy all aspects of a 'normal' Congress, including the chance to talk about science with friends and colleagues and to enjoy real life, something we all miss very much.

Daniela Cota
e-ECE 2021 Basic Science Co-Chair

Lars Rejnmark
e-ECE 2021 Clinical Co-Chair

Riccarda Granata
ESE Congress Committee Chair

Executive Committee update

We welcome Jérôme Bertherat (France) as ESE President-Elect, Martin Fassnacht (Germany) as Chair of the Science Committee, and Philippe Chanson (France) as Chair of the Publishing and Communications Committee. Grateful thanks are due to retiring Chairs Felix Beuschlein and Beata Kos-Kudta.





EDCs – an issue for us all

Chemicals identified as endocrine disruptors (EDCs) are still widely produced, distributed and omnipresent. They are found in the environment, terrestrial and aquatic lifeforms, and humans. European citizens are in contact with many EDCs contained in various articles for daily use.



Endocrinologists worldwide have provided solid scientific evidence, epidemiological data and large cohort and case control studies demonstrating that local or global exposure to individual EDCs or their mixtures is associated with adverse health effects for individuals or populations. Such human health-related observations on adverse EDC effects receive strong scientific support from *in silico*, *in vitro*, animal experimental and mechanistic data, all demonstrating clear cause-effect relationships related to the extent and duration of EDC exposure.

ESE's and our sister societies' scientific journals publish thematic issues or single articles containing EDC-related basic, translational, epidemiological and clinical practice-focused data.

Against this background, it is likely that you, just like many other endocrinologists (including ESE's EDC Working Group), agree that urgent EDC-related health issues do not yet receive adequate attention or action in a far-sighted European health policy.

Action against inaction

The current sad situation of slow environmental reform is illustrated by the following examples.

- A group of young people recently had to exact a clear decision by the German Federal Constitutional Court to force the German Government to stipulate a climate path conforming to ambitious climate objectives.
- The Dutch environmental organisation Milieudefensie had to sue a Dutch-British oil company to accelerate measures to reduce its CO₂ emissions and exploitation of fossil fuels, while speeding up utilisation of renewable energy.
- Several European governments, the European Parliament and the European Council had to sue the EU Commission regarding its failure to adopt scientific criteria for the determination of properties of EDCs by 2013, and to enact such legislation and regulation, following two decades of inactivity.

Positive steps

In this context, publication by the EU Commission of the *Chemicals Strategy for Sustainability Towards a Toxic-Free Environment (CSS)* in October 2020 was a major step forward. This document points in the right direction in the context of the European Green Deal. We eagerly await its full and immediate implementation to secure the 'precautionary principle' codified in Article 191 of the EU Treaty agreed in Lisbon in 2007.¹

The CSS announces, among other points:

- legally binding hazard identification of EDCs
- inclusion of EDCs as a new hazard category of 'substances of very high concern'
- phasing out of EDCs in consumer products.

'As endocrinologists, you and I are the experts on hormones and EDCs. We all need to play our part now'

The EU Commission correspondingly updated the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals, 2006) and CLP (Classification, Labelling and Packaging, 2008) roadmaps in May 2021, which now include the new EDC hazard class, added to the previously established CMRs (carcinogenic, mutagenic and reprotoxic substances). This is a game changer for regulatory processes.

Words alone are not enough

Yet, publishing the CCS is definitely not sufficient! Now, it is time for the EU Commission to deliver – as we know very well, 'paper is patient'. Implementing binding provisions linked to enforcement, monitoring and efficient control is required.

'Safer' mixture factors for EDCs in hazard identification and subsequent risk assessment need to be incorporated, because we are not only exposed to single EDCs but to broad mixtures. Special consideration is due to those with long half-lives, and so-called 'legacy EDCs'. Albeit forbidden or phased out decades ago, they remain in our environment, ecosystems, food chains and articles of daily use.

Opposing forces

We need to be aware of and prepared for continuous opposition from various interest and lobbying groups, using tracks and networks well established during the last four decades. They effectively refused changes and successfully prevented immediate reduction of EDC exposure or implementation of bans for the most critical chemicals on the long list of identified and suspected EDCs.

These opposing actions will come from industry, supported by various sectors of the European economy, demanding (for example) 'impact assessment' of measures. Further assertion would put health issues, prevention and precaution in the back seat, while market power would occupy the driver's seat. Experience has shown that prioritising the 'self-regulating market' results in no change (as seen with bisphenol A and other regrettable EDC substitutes). Products, processes and technologies will be declared 'essential for survival', albeit continuing to cause harm to population and environment.

Therefore, EDC regulations need to be horizontal and intersectoral. A chemical cannot be declared an EDC when used for one purpose (e.g. as a pesticide) but not another (a constituent of a toy). As Gertrude Stein might have said, if writing in 2021, 'An EDC is an EDC is an EDC'!

We are the experts and we must act

As endocrinologists, you and I are the experts on hormones and EDCs. We all, regardless of age, nationality or career stage, need to play our part now.

- We must communicate our knowledge to patients, especially to young parents concerned about EDC effects on development of their children.
- We should provide our expertise by advising regulatory authorities, politicians and the media.

In seeking action on EDCs, we must demand urgent answers...

- Which steps will the EU Commission implement first?
- What information, data and procedures are needed to implement a reduction in EDC exposure?
- Will the EU Commission increase EDC research funding for up-to-date test methods, including endocrine areas other than EATS (oestrogens, androgens, thyroid, steroids), which have not been addressed?
- How can ESE members support the EU Commission's aims in the CSS?
- How can we provide expertise against strong pressure groups or opposing EU member states in the EU Council?

As endocrinologists, we must strive for an economy that is safe and sustainable, avoiding snowballing exposure to suspected and identified EDCs. We must act without further delay!

Josef Köhrl

Chair, ESE EDC Working Group, and Environmental Endocrinology Focus Area Lead

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1. EUR-Lex 2021 <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:132042>.



In vaccines we trust

Alojz Ihan is Professor of Microbiology and Immunology at the Faculty of Medicine of the University of Ljubljana in Slovenia. He provides us with an immunologist's view of the future course of the COVID-19 pandemic, and emphasises the importance of building trust and confidence in vaccination amongst all patients.

The COVID-19 pandemic has caused one of the biggest global health, economic and social crises of the last century. Generations born in the second half of the 20th century could not have imagined an epidemic that would stop life on the planet to such an extent. Could anyone have envisaged, just 2 years ago, why the whole world would suddenly stop travelling by plane and ship, and why tourism, sports, events and entertainment would shut down?

The pandemic is not just a medical phenomenon. The social consequences of epidemic containment define an epoch that has seen what is probably the most expensive social intervention in history, with the exception of world wars.

This is due to the properties of a new coronavirus, SARS-CoV-2: high infectivity, a more severe course of disease with a frequent need for respiratory support in 20% of patients, and uncertain immune protection after overcoming the illness. Without an effective drug, a health catastrophe can only be prevented by epidemiological containment of the epidemic. As a rule, this brings great economic and social damage, especially in cases where the epidemic is on the rise and long term, months-long, intensive containment measures are needed to calm it down.²

Vaccines offer hope

The development and use of effective COVID-19 vaccines offer the only realistic hope that the epidemic will not recur in the next cold season to the same extent that we are experiencing now, with deepening of all its social and economic consequences. However, the vaccines must be used to a sufficient extent, as only proper vaccination can stop the epidemic.

With mass vaccination, we expect a reduction in cases of severe disease. How effectively vaccines can reduce transmission, however, will be seen in the future. Data from clinical trials suggest that the vaccines that prevent symptomatic infection could also prevent transmission. A vaccine that is 90% effective in preventing the transmission of the virus will need to reach at least 55% of the population to achieve temporary herd immunity, taking into account all basic protective measures (protective masks, distance, ventilation, etc.). To remove all protective measures, however, about 67% of people would need to be vaccinated to ensure herd immunity.

In many countries, vaccination covering at least 50% of the population will be very demanding to achieve. If vaccination is not widespread enough in certain parts of the world, there will be constant foci of new infections and, above all, permanent opportunities for the development of new versions of the virus, with the looming danger of vaccine resistance and fading immunity.



What does the future hold?

Given all the circumstances, it is not yet clear whether COVID-19 will become a chronic seasonal disease. There is too much uncertainty about the likelihood and frequency of new variants and a reduction in vaccine efficacy, especially against existing variants (such as those from South Africa and India) and potentially new mutants. Predictions of cross-immunity in humans are unclear, and the consistency of our safe behaviour is constantly on test.

There is a chance that the new coronavirus will follow a similar path to influenza – with outbreaks in the cold winter months. It is likely that COVID-19 will become an endemic, but less important, seasonal infection in many regions of the world. This is especially likely in more developed areas, due to vaccination quickly taking into account possible new variants of the virus.

In countries and regions where vaccination and public health measures to contain the epidemic are not and will not be good enough, important foci of infection will remain. However, we anticipate that in countries with good vaccination, there will be no recurrence of epidemics.

Possible recurring seasonal COVID-19 is likely to require a change in the healthcare system and a thorough adjustment to life, which will be especially true for vulnerable people during the winter months. It is essential to prepare for such a scenario by co-ordinating epidemiological surveillance and monitoring programmes for local epidemics (in addition to the pandemic), as well as more appropriate public health activities, primary and hospital healthcare organisation and socio-economic programmes in the long term.

'We need to make it clear that vaccination is safe and the only appropriate solution. We need to be especially responsible and precise in explaining the benefits and potential risks to different groups of patients'



The importance of vaccine confidence

An essential element of any vaccination policy is people's confidence that the vaccination is safe and effective. They must believe that each vaccinated individual will gain health benefits and contribute towards solving a huge common health and societal problem that has been crippling life for a year and will continue to cripple it without effective vaccination. Such confidence is the foundation of the final phase of overcoming the epidemic.

Trust, however, is first and foremost based on clear and objective information. We need to make it clear to each group of people that vaccination is safe and the only appropriate solution. We need to be especially responsible and precise in explaining the benefits and potential risks of vaccination to different groups of patients. On the one hand, patients with chronic disease are particularly receptive to quality health information but, on the other hand, vague medical explanations quickly put them in doubt.

We immunologists are faced with dozens of questions about COVID-19 vaccination on a daily basis. That includes enquiries from many long term patients with weakened immune systems, autoimmune diseases or cancer, or patients on various immunosuppressive therapies. Patients want to know whether it's safe to get vaccinated and, if they do, which vaccine should they get? And of course, they also have concerns about how it can affect their own condition as well.

Although vaccine registration studies, typically performed on 30 000–40 000 people, also provided information on the safety and efficacy of vaccines in chronic patients, there are still insufficient data to provide clear and specific answers to all patient groups. Many questions asked by patients will remain unanswered for some time to come, but we can be convincing about the basic answer: getting COVID-19 is significantly more risky than getting vaccinated.

Meanwhile, it is our job to check the effects of vaccination on all groups of patients, as each patient deserves an answer to what vaccination means for their disease. And it is our medical duty to give all the answers we can provide to our patients as soon as possible.

Alojz Ihan

Institute of Microbiology and Immunology,
Medical Faculty of Ljubljana, Slovenia



'Many questions asked by patients will remain unanswered for some time to come, but we can be convincing about the basic answer: getting COVID-19 is significantly more risky than getting vaccinated'

ESE statement on COVID-19 vaccination

This statement, issued in February 2021, urges healthcare providers **to follow the same recommendations for patients with stable endocrine disorders as for the general population.** It is available on the ESE website at www.ese-hormones.org/esestatementconcerningcovid19vaccination.

It has come to ESE's attention that patients with endocrine disorders like autoimmune thyroiditis have been declined to receive a COVID-19 vaccination. This has prompted ESE to release the following information.

Trials that have led the European and US health authorities (the EMA and FDA) to authorise the first two vaccines included more than 40 000 and 30 000 volunteers respectively, aged from 16 to over 75 years of age. Among them were patients with diabetes, obesity, malignancies, HIV, chronic pulmonary disease, as well as cerebrovascular and liver disease, in a stable health condition. Efficacy and safety in these patients were comparable with healthy subjects. In addition, the US Centers of Disease Control and Prevention state that persons

with autoimmune conditions who have no contraindications to vaccination may receive an mRNA COVID-19 vaccine.

ESE therefore stresses that the recommendation for COVID-19 vaccination in patients with stable endocrine disorders like autoimmune thyroiditis, Graves' disease, Addison's disease, pituitary adenomas, diabetes type 1 and 2 and obesity should not be different from the one for the general population. Patients with adrenal insufficiency should be informed that, in case of side effects like fever, sick day rules should be followed.

Anton Luger

ESE Executive Committee member responsible for ECAS

Andrea Giustina

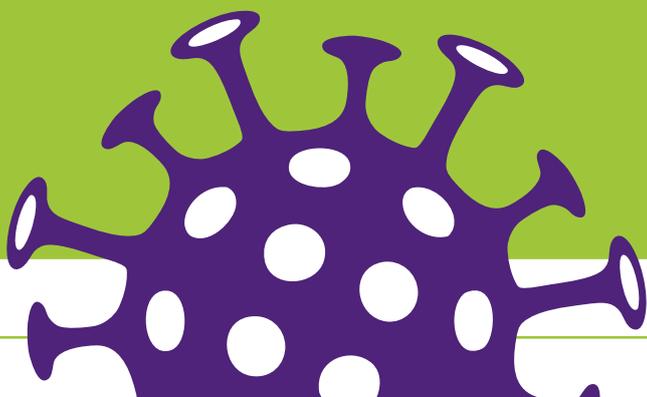
ESE President (at the time of writing)

Robin Peeters

ESE Clinical Committee Chair, on behalf of the Clinical Committee



European Society
of Endocrinology





The increasing prevalence of autoimmune disease

Autoimmune disease has become more common in recent decades. Sari Mäkimattila examines some of the factors that are likely to be involved.

Autoimmune diseases (ADs) comprise over 80 chronic disorders, in which the immune response to self-antigens results in damage to or dysfunction of the target organs.¹ The pathogenesis is not understood completely, but genetic and environmental factors are involved. Alteration of microbiome 'dysbiosis' as well as viral infections can induce AD in people with certain genetic backgrounds. Also, stress-triggered neuroendocrine and adrenal hormones may lead to immune dysregulation that results in AD.²

An estimate for the worldwide incidence of ADs is 3–7%, but the incidence and prevalence have been increasing over the last 30 years, especially in developed countries and in migrant populations.³ These observations point to a stronger influence of environmental factors on AD development, as opposed to genetic factors.

Likely associations with environmental agents

Bacteria and microbial products regulate the development and function of the immune system.⁴ Evidence is accumulating that the crosstalk between the intestinal microbiota and the immune system is modulated by nutrition. Their interplay involves a complex network of transcriptional, genetic and epigenetic programmes. The incidence of immune-mediated diseases is elevated in countries where the diet contains a high intake of total calories, fats, sugars and nitrites, a low intake of fibre and imbalanced fatty acid composition that may induce inflammation and lead to low microbial diversity.⁴ Gluten ingestion causes coeliac disease. No other associations between dietary factors and ADs have the same level of confidence.

However, certain macronutrients (lipids such as omega-3 fatty acids), micronutrients, phytochemicals and functional foods (probiotics) may impact the immune system by preventing or having therapeutic potential for ADs.^{5,6} Vitamin D deficiency and a decrease in the serum levels of selenium and zinc have been noted in patients with ADs,^{7–9} which may be a risk factor for inflammation and initiation of autoimmunity.

Accumulation of ADs within the same individuals

ADs often appear within the same families, and some individuals accumulate several ADs.¹⁰ Why this is so is not completely understood, but there appears to be a multi-factorial cascade that relates to genetics and interaction of lymphocytes and antigens, as well as external factors such as viruses. These may need to be present during certain periods of life, or in a specific sequence, to induce the immune perturbations that result in AD.

There is a genetic overlap in the human leucocyte antigen (HLA) region as it encodes several molecules that play key roles in the immune system.^{11,12} This may explain why every fifth individual with type 1 diabetes suffers from at least one other AD, and their excess risk of concomitant ADs compared with the general population is manifold.¹³ Coeliac disease and hypothyroidism are the most frequently observed additional ADs in type 1 diabetes, followed by gastric autoimmunity, vitiligo, hyperthyroidism, autoimmune adrenalitis, gonadal insufficiency, autoimmune hepatitis, dermatomyositis and myasthenia gravis.

'The incidence and prevalence of autoimmune diseases have been increasing over the last 30 years, especially in developed countries and in migrant populations. This points to a stronger influence of environmental, as opposed to genetic, factors'



In general, female sex, older age at the time of diagnosis and longer duration of type 1 diabetes confer a greater risk of multiple ADs.^{13,14} The risk of coeliac disease, however, is greater among those diagnosed with diabetes at the age of 10 or less, having an immature immune system. A possible mechanism might be coexpression of antigens from both diseases in the same anatomic location. Transglutaminase autoantibodies are known to be overexpressed in stressed islets. As the duodenum and pancreas are in close proximity and share draining lymph nodes, insulinitis may promote coeliac disease autoimmunity.¹⁵

For most ADs, females are five to six times more often affected than males. There may be gender differences in immune response, organ vulnerability, reproductive capacity, sex hormones, genetic predisposition or parental inheritance.¹⁶ However, the incidence of type 1 diabetes is higher in males than in females,¹⁷ and the sex differences for additional ADs are less pronounced compared with the general population.¹³ The reason for this may be that pancreas islet autoimmunity increases the risk of other ADs by overruling the sex-specific immune reactivity.¹⁶

In conclusion

Clinicians strive to provide answers to their patients, but there are still many unanswered questions related to the increased incidence of ADs. New cell biological methods combined with data from clinical and epidemiological research may give information which could have an impact on the prediction, mitigation and, ideally, even the prevention of ADs. Meanwhile, it is important to screen for other autoimmune diagnoses if subjects with type 1 diabetes or another AD present with new or non-specific symptoms.

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Novel genetic associations in autoimmune Addison's disease

Mapping the important genes in autoimmune Addison's disease (AAD) has indicated a complex network of antigen presentation and immunomodulation, and the importance of central immune tolerance in AAD pathogenesis.

The rarity of autoimmune adrenal insufficiency has, until now, made scanning the whole genome for disease variants difficult. However, combining the Swedish and Norwegian Addison registries has made the first genome-wide association study (GWAS) possible.

In a paper recently published in *Nature Communications*,¹ research teams from Karolinska Institutet (Sweden) and the University of Bergen (Norway) report 10 independent risk loci for AAD using 1223 AAD cases who were positive for 21-hydroxylase autoantibodies and 4097 controls. Some of the loci were known previously and are shared with other organ-specific endocrinopathies (*HLA*, *BACH2*, *PTPN22*, *CTLA4* and *AIRE*), but others were novel (including *LPP*, *SH2B3*, *SIGLECS* and *UBASH3A*) (Figure). Altogether, about 40% of the heritability of AAD is explained by the findings in this GWAS study.

The *AIRE* gene

Of particular interest was a strong association with two protein-coding alterations in *AIRE* (autoimmune regulator). The strongest, p.R471C, introduces an extra cysteine residue in the zinc finger motif of the second PHD domain, which could alter the function of *AIRE*.

Mutations in *AIRE* are otherwise known to cause autoimmune polyendocrine syndrome type 1 (APS-1), characterised by early onset organ-specific autoimmune manifestations.² AAD is one of three main manifestations, together with hypoparathyroidism and chronic mucocutaneous candidiasis. *AIRE* is a transcriptional regulator expressed in thymic medullary epithelial cells. It plays a key role in shaping the T cell repertoire by facilitating the expression of organ-specific proteins, not usually found in the thymus. Developing T cells with reactivity against self-proteins are purged from the immunological repertoire or transformed to T regulatory cells. When *AIRE* is not functional, autoreactive T cells escape to the periphery with the potential to cause organ-specific autoimmunity later in life.

How the Addison-associated variant R471C affects the function of *AIRE* is, at present, not known, but it is reasonable to assume that *AIRE*'s functional capacity is reduced to some degree. However, since the allele frequency of R471C is 1.5–2.0% in the general population, the effect must be smaller compared with the mutations causing classical APS-1.

Other associations

The human leucocyte antigen (HLA) region revealed by far the largest risk for AAD compared with other associated loci. This was dominated by HLA class II, but also with clear associations with HLA class I. HLA class II presents antigens to developing T cells, and the combination of DR3–DQ2 and DR4–DQ8 confers an approximately 30 times increased risk of AAD.

Other associations include the immune checkpoint *CTLA4*, which modulates the co-stimulation required for T cell activation. The turnover of the T cell antigen receptor complex is regulated by *UBASH3A*, another risk locus identified in the study. *SH2B3*, which might explain the common autoimmune *ATXN2/SH2B3* association, is an inhibitor of signalling cascades in lymphocytes. Association with *LPP*, which contains a microRNA (miR-28), appears to be involved in post-transcriptional regulation of PD1, playing an important role in self-tolerance, restraining autoreactive T cells and promoting T regulatory cells. Interestingly, there are several case reports describing AAD caused by immune checkpoint PD1 inhibitors with 21-hydroxylase autoantibodies.

Significance for AAD management

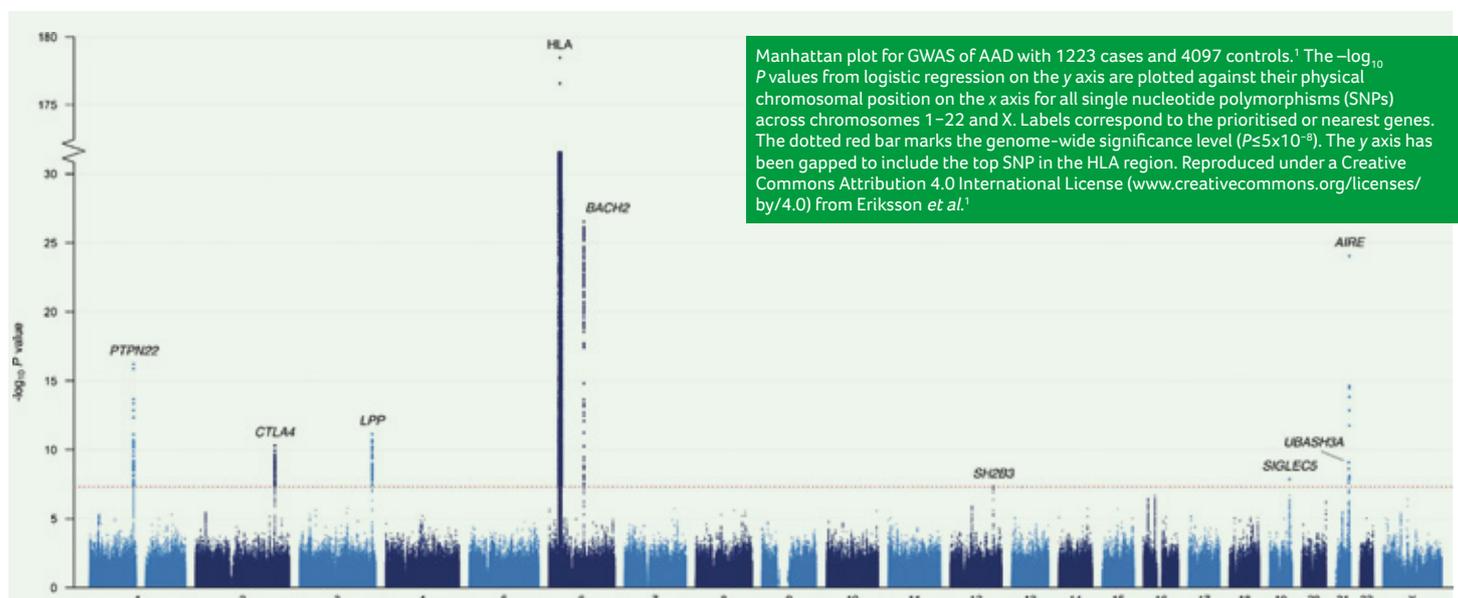
What are the implications for the patients and physicians treating AAD patients? The findings point to aberrations in central immunological tolerance, which could guide future treatment aimed at protecting any residual adrenocortical function. Several studies have shown that up to 30% of patients retain some endogenous corticosteroid secretory capacity.³ Rituximab treatment that targets B cells has had limited effect.⁴ The GWAS results indicate that a drug modulating T cells might be more effective. Furthermore, the new knowledge on genetic associations should enable us to develop better tools for prediction of development of AAD.

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Manhattan plot for GWAS of AAD with 1223 cases and 4097 controls.¹ The $-\log_{10}$ P values from logistic regression on the y axis are plotted against their physical chromosomal position on the x axis for all single nucleotide polymorphisms (SNPs) across chromosomes 1–22 and X. Labels correspond to the prioritised or nearest genes. The dotted red bar marks the genome-wide significance level ($P \leq 5 \times 10^{-8}$). The y axis has been gapped to include the top SNP in the HLA region. Reproduced under a Creative Commons Attribution 4.0 International License (www.creativecommons.org/licenses/by/4.0) from Eriksson *et al.*¹



COVID-19: endocrine–metabolic complications



Sandro La Vignera

The 2019 coronavirus outbreak, caused by SARS-CoV-2, has focused researchers' interest on understanding the disease's pathogenesis, treatment and complications. So, what are the possible long term endocrine–metabolic effects in COVID-19 patients?

Comparison with SARS

Knowledge of the long term complications associated with SARS-CoV, the aetiological agent of SARS in 2003, may be useful in identifying similarities with SARS-CoV-2.¹

SARS-CoV is known to directly damage pancreatic cells, due to their high expression of angiotensin-converting enzyme 2 (ACE2). Pancreatic damage causes transient or permanent diabetes. Additionally, SARS-CoV has been isolated in the adrenal and pituitary glands of SARS patients, thus providing evidence of the virus's ability to infect these endocrine glands and, possibly, alter their function. In fact, some studies have reported that the adrenal response to the adrenocorticotrophin stimulation test is suboptimal in patients with SARS, although there are no definitive data. Some have reported the presence of central hypothyroidism in SARS survivors, suggesting that SARS-CoV alters pituitary function. Finally, this virus appears to harm gonadal function, mainly due to testicular expression of ACE2.¹

Discoveries in COVID-19

This evidence sheds light on the possible long term complications of COVID-19. SARS-CoV-2 is, in fact, capable of damaging various organs via an autoimmune mechanism. Therefore, the onset of autoimmune endocrinopathies such as thyroiditis, adrenalitis, etc. could be predicted in COVID-19 patients.¹

Consistent with this, subacute thyroiditis has been reported in COVID-19 patients after resolution of the acute phase of the disease.² ACE2 expression in the thyroid gland appears to be the main mechanism by which SARS-CoV-2 infects thyrocytes, and active viral replication induces their lysis.² A recent study also explored the impact of SARS-CoV-2 infection on the hypothalamic–pituitary–adrenal (HPA) axis, concluding that there

was impaired function of central origin in the patients studied.³ ACE2 is expressed in both the adrenal and the pituitary glands, thus providing an explanatory mechanism for these effects.

ACE2 is also expressed in the testis, and it has been suggested that long term hypogonadism could potentially occur in SARS-CoV-2-infected patients.⁴ Indeed, serum levels of luteinising hormone and total testosterone (TT) were found to be significantly lower in 286 symptomatic male patients with laboratory-confirmed COVID-19, when compared with healthy men. Lower TT levels also predicted the patients' clinical outcomes.⁵

Taking all this into account, a long term endocrine follow-up of COVID-19 patients should reasonably include the evaluation of the thyroid, the HPA axis and gonadal function. However, further research is still needed, including assessment of pancreatic function after COVID-19 recovery.

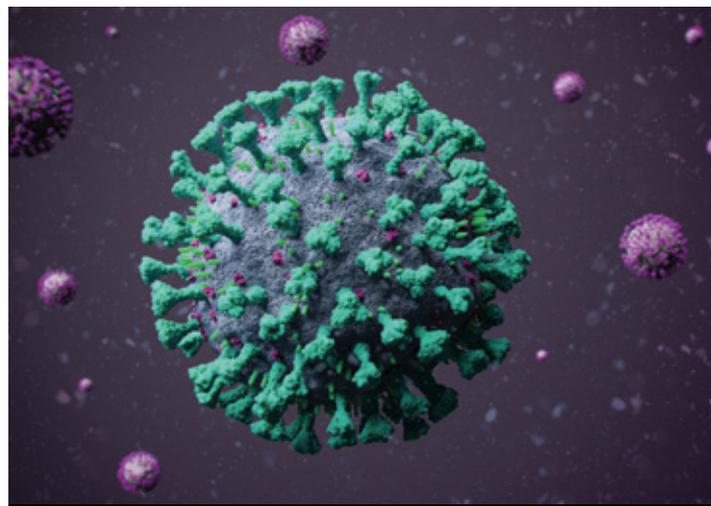
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Meet Adrian Clark

Endocrine
CONNECTIONS 



Adrian JL Clark became Editor-in-Chief of open access journal *Endocrine Connections* at the start of 2021. Here, he tells us about himself, his passion for endocrinology and his vision for the journal and the future of science publishing.

Please tell us about your current work

I have retired from full-time endocrinology, but still maintain strong research links with the Centre for Endocrinology and the William Harvey Research Institute at Barts and the London. I have also been fortunate to have a role as Chairman of Bioscientifica for the last 4 years. I have a broad spectrum of interests in endocrinology, although my main interest is in adrenocorticotrophin (ACTH)'s action on the adrenal.

Who first inspired your interest in endocrinology?

As a medical student, I was attached to the Department of Endocrinology at Barts at a time when it supported an incredible array of young talent led by Mike Besser – one of the best teachers I know – and including Lesley Rees, Mike Thorner, Chris Edwards, Phil Lowry, John Landon and Tim Chard, amongst others. At the time, endocrinology seemed to be the only branch of medicine that offered any sort of precision in diagnosis or treatment.

What has been most satisfying about your work?

Nothing beats discovery – finding something that nobody has found before. I liken it to being an early explorer landing on a foreign shore and not knowing what is beyond the beach. I have been lucky to be involved in many exciting discoveries – mostly fairly trivial, but nevertheless thrilling. Discovering that the ACTH receptor was mutated in an inherited adrenal disorder called familial glucocorticoid deficiency, and then, over the following 15 years, finding another five genetic defects that led to the same clinical outcome has been my main achievement.

What sets *Endocrine Connections* apart from other journals?

Endocrine Connections was conceived as a novel attempt to support the development of connections within endocrinology and between endocrinology and other disciplines. Such cross-fertilisation is essential in my view for a subject to develop. This feature, combined with the fully open access format and some of the lowest article processing charges for an established journal, should make this the obvious place to publish – as well as the fact that all profits support its parent societies, ESE and the Society for Endocrinology.

‘Nothing beats discovery – finding something that nobody has found before. I liken it to being an early explorer landing on a foreign shore and not knowing what is beyond the beach’

How would you like to see the journal develop?

There are a multitude of connections within endocrinology that could be exploited more effectively. One example amongst several is the separation of adult and paediatric endocrinology – which are often located in different departments in many institutions. I believe there are also many lessons and techniques to be learnt from immunology, neuroscience or vascular biology, for instance, that we should take advantage of. If the journal can find the way to really achieve this, I will be very happy.

What are the greatest challenges for journals currently?

There are several. One is maintaining quality peer review at a time when institutions are (quite reasonably) demanding greater value for money from their employees. Another is avoiding the rejection of good science because of an author's poor command of written English. Then there is overcoming the data reproducibility problem, and escaping the tyranny of the backward-looking impact factor.

‘There are a multitude of connections within endocrinology that could be exploited more effectively. One example is the separation of adult and paediatric endocrinology’

What do links to a learned society mean for a journal in 2021?

Scholarly publishing functions on a unique model in which all the financial benefits pass to the publisher. Would Taylor Swift or James Patterson or Stephen Spielberg have worked on that basis? The model is unlikely to change very soon but, so long as the publishers are, effectively, societies that support the development of our field, I believe that is a perfectly acceptable solution. In turn, it is important that society members see the journal as ‘their journal’, considering it first when preparing a publication, and supporting it through peer review when invited.

Has the pandemic affected scientific publishing's future?

Undoubtedly it has in the short term. Clinicians have been overwhelmed and laboratories and core facilities have been closed for long periods. In some cases, there has been an opportunity for some unwritten papers to be completed, leading to a short-lived wave of such papers, but it is likely that new work will then wane for a time. In the longer term, I hope that the focus on COVID-19 has advanced the case for making peer-reviewed research as widely accessible as possible, although I am less enthusiastic about the pandemic's promotion of preprint publication.

What else do you hope will change following the pandemic?

Greater respect for science and medicine, and the inspiration to young people that this will provide.

Find out more about *Endocrine Connections*, including the 40% reduction in article publication charges for ESE and Society for Endocrinology members, at <https://ec.bioscientifica.com>.



Testing thyroid function in COVID-19

EJE Clinical & translational endocrinology from around the globe

This recent paper in *European Journal of Endocrinology*¹ examines the spectrum of thyroid function tests in patients during hospitalisation for SARS-CoV-2 infection.

The thyroid gland may be affected by COVID-19, and cases of subacute thyroiditis have been reported, occurring after the resolution of the infection. Moreover, in hospitalised COVID-19 patients, several changes in thyroid function tests (TFTs) may occur, but data might be biased.

Treatments influence the levels of thyrotrophin (TSH) (steroids, dopamine), free thyroid hormones (anti-epileptic drugs) or both (steroids, contrast media). Baseline data might be inaccurate, because therapies administered before admission are often unknown. Free thyroxine (FT4) immunoassays are prone to artefacts when binding proteins are altered by drugs, non-thyroidal illnesses, or changes in thyroxine-binding globulin/albumin due to sepsis. In addition, COVID-19 patients have hypoalbuminaemia which increases the risk of artefactual hyperthyroxinaemia by heparin, and thyroid imaging is very often unavailable because of restrictions for safety concerns.

Reviewing the data

In our recent study,¹ we reviewed the longitudinal data of 144 COVID-19 patients who were consecutively enrolled between March and May 2020, including critical cases, with an overall mortality rate of 25%.

We were extremely careful to avoid causes of interference by excluding patients with thyroid diseases and/or taking interfering drugs, while those treated with corticosteroids (CS) were analysed separately. All serum samples were taken more than 10 hours after the administration of heparin as prophylaxis for embolism. For stored samples, we retrospectively measured thyroglobulin antibodies and thyroglobulin at the time of TSH suppression and cortisol levels at baseline and during follow-up, in patients not taking CS.

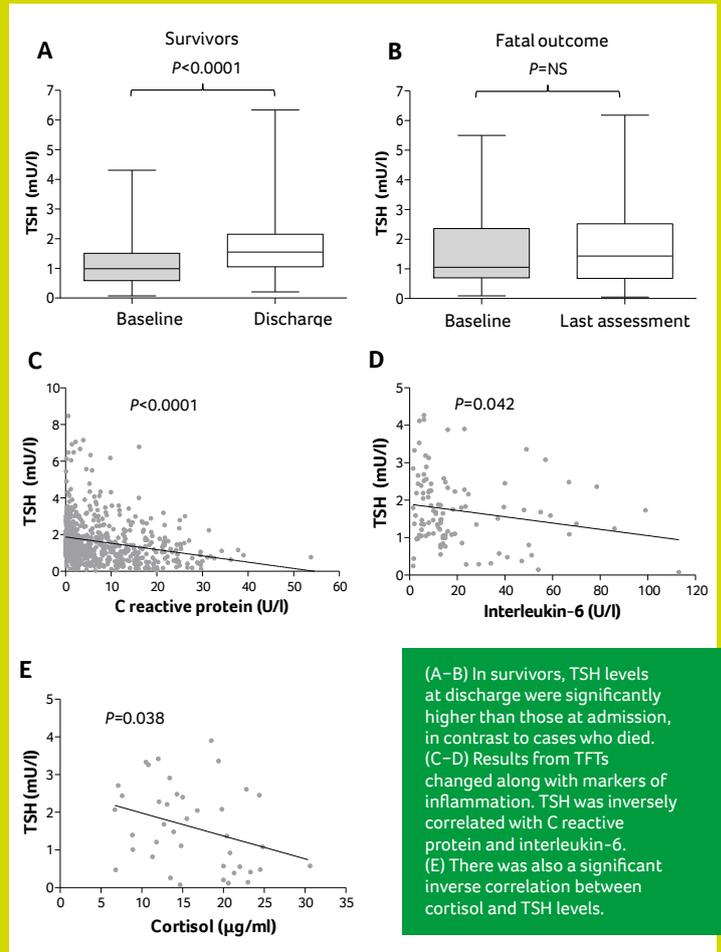
Our findings

The main findings are summarised in the Figure. In our cohort, all patients with overt hyperthyroidism had primary thyroid diseases. On the other hand, 10.4% of patients without history of thyroid dysfunction had low TSH levels at admission, while 23.5% developed TSH levels $<0.4\text{mU/l}$ during hospitalisation, most of them (77%) following CS administration. Notably, 43% had TSH levels $<0.2\text{mU/l}$ at admission or during the follow-up, whereas a smaller reduction (≥ 0.2 but $<0.4\text{mU/l}$) was found in the remainder. Most (23/39) had also low levels of free tri-iodothyronine (FT3), 10 of whom were on CS. Low FT3 and FT4, with low or normal TSH, were found in 12 critically ill patients.

Longitudinal evaluation during the hospital stay showed that TSH suppression was transient in survivors, with a mean \pm SD time to normalisation of 4.26 ± 1.98 days (range 2–9), whereas TSH and FT3 were permanently low in most of the cases who subsequently died.

We found that thyroglobulin was normal at the time of TSH suppression, thus excluding thyrotoxicosis. Indeed, if the TSH suppression had been the result of a destructive thyrotoxicosis, the preformed thyroglobulin would have increased. Interestingly, TSH fluctuations were also found in two thyroidectomised patients, indicating that they were independent of thyroid hyperfunction/destruction. TSH levels at discharge were significantly higher than those at admission in survivors, in contrast to cases who died (Figure A–B). This appeared not to be due to an effect of CS, as it was observed in patients with or without CS treatment.

TFTs changed along with markers of inflammation. Indeed, TSH and FT3 were inversely correlated with C reactive protein and with pro-inflammatory cytokine interleukin-6 (Figure C–D). This finding is



Insights from the Editor

There is certainly much more that is unknown than known with regard to COVID-19 infections. Researchers around the globe are currently contributing to our knowledge regarding pathogenesis, diagnosis, prognosis and treatment efficacy of the disease. In their turn, many important research questions regarding the interplay between COVID-19 and hormonal systems or endocrine diseases will have to be examined. Not surprisingly, hormonal alterations will occur during COVID-19 infections, and these alterations are likely to be more pronounced in patients with more severe disease.

The study by Campi *et al.* that is highlighted here attempts to explore the effect of COVID-19-induced cytokine release on thyroid hormones. The authors found a low thyrotrophin level in many patients, either at admission or during follow-up. This phenomenon was mostly transient.

The study does not answer the question of whether thyroid hormones play a causal part in the course of the disease, or whether they are merely a marker of COVID-19 disease severity. But it emphasises that endocrine systems are centrally affected by and involved in COVID-19 infections. Given this central role, more research in this direction will probably follow soon.

Olaf Dekkers

Deputy Editor, *European Journal of Endocrinology*



consistent with the known effects of cytokines, which are usually found to be elevated during viral infections, on TSH suppression. Similarly, we found a significant inverse correlation between cortisol (which increases in stressful events) and TSH and FT3 levels (Figure E).

In conclusion

Taken together, our data suggest that the cytokine release associated with SARS-CoV-2 causes changes in TFTs. During the hospitalisation period, the slight reduction in TSH with normal FT4 levels and low-normal FT3 levels should be interpreted as a change in peripheral thyroid hormone metabolism and/or pituitary responsiveness rather than linked to thyrotoxicosis, which could, instead, develop a few weeks after discharge.

Irene Campi

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COVID-19 patient data in EuRRECa

The European Registries for Rare Endocrine Conditions (EuRRECa, www.eurreca.net) joined forces with Endo-ERN and the ESE Rare Disease Committee in spring 2020, to gather data on COVID-19 infection in chronic endocrine or bone disease (*ESE News* issue 43). The initial data have been collated.

24 centres
have submitted

194

COVID-19
cases

Made up of
164 adults
30 children

These include
72 pituitary patients
54 adrenal patients
24 genetic endocrine
tumour patients

Continued rise in Impact Factors



European Journal of Endocrinology's 2020 Impact Factor is its highest ever. A 25.5% increase to 6.664 puts it at 20 out of 145 in the Endocrinology and Metabolism category of the new Journal Citation Reports (compared with 23 out of 143 last year). The Impact Factor has increased steadily since 2012 when it was 3.791.

Endocrine Connections' Impact Factor has also risen, by 28.7% to 3.335. The journal is now ranked 94th out of 145 journals (last year it was 96th out of 143).

This growth is the result of the dedication and hard work of past and current Editors-in-Chief and Editorial Board members, high quality contributions by authors, and the global effort of field-leading reviewers.

ESE's President, Martin Reincke, said 'The 2020 Impact Factors are a milestone for the Society – we are all immensely proud of our journals. *European Journal of Endocrinology* underpins ESE's role as the voice for endocrinology in Europe and our mission of advancing endocrinology. *Endocrine Connections* continues to gain valuable traction as a key journal for dissemination of endocrine research.'



'The Rare Disease COVID-19 Task Force was ESE and Endo-ERN's first joint initiative. It led to collection of data from COVID-19 patients with a rare endocrine condition, showing the great value of these activities in enhancing research and patient care.'

Simona Glasberg, co-Chair of the ESE Rare Disease Committee with Alberto Pereira



'Fortunately, e-REC, a rare disease surveillance platform developed to support Endo-ERN, could be quickly adapted to meet this need. Please participate in the COVID-19 project by submitting your data, or using the data we have collected.'

Faisal Ahmed, EuRRECa Co-ordinator

A field for vaccination status has now been added to follow-up questionnaires. Submit your data and find out more at www.e-se-hormones.org/research/eses-research-programmes/rare-disease-covid-19-task-force.

See abstract OC14.5 at e-ECE 2021 at www.endocrine-abstracts.org/media/12974/ece2021abstractbook.pdf.





Celebrating success at e-ECE 2021

Honorary Member



Honorary Membership of ESE was awarded to **AJ van der Lely** (The Netherlands). AJ was President of ESE from 2015 to 2019 and had previously served as Treasurer. He is Professor of Endocrinology at the Erasmus University Medical Center in Rotterdam.

Honorary Membership is awarded to individuals of special distinction in endocrinology or those who have performed outstanding service to the Society.

Special Recognition Awards



Justo Castaño (Spain) and **Sofia Llahana** (UK) received Special Recognition Awards at e-ECE 2021. Justo was recognised for his extremely valuable contribution and engagement in the Society's activities. Sofia received the award for her dedication to ESE through substantial development of nurse activities in Europe through the Nurse Working Group (now the Nurse Committee).

Award Lecturers



Niels E Skakkebaek
(Denmark)
European Hormone Medal



Vera Popovic-Brkic
(Serbia)
Geoffrey Harris Award



John Wass
(UK)
Geoffrey Harris Award



Ruben Nogueiras
(Spain)
European Journal of Endocrinology Award



Rosario Pivonello
(Italy)
Clinical Endocrinology Trust Award



Panagiotis Anagnostis
(Greece)
Jens Sandahl Christiansen Award

Young Investigator Award winners

The 2021 recipients are **Anastasia Arvaniti** (UK), **Márcia Faria** (Portugal), **Vittoria Favero** (Italy), **Antonio C Fuentes-Fayos** (Spain), **Julia Krupinova** (Russia), **Georgios Markantes** (Greece), **Narjes Nasiri-Ansari** (Greece), **Claudia Pivonello** (Italy), **Roby Rajan** (UK), **Prudencio Sáez-Martínez** (Spain), **Valentine Suteau** (France) and **Frederique Van de Velde** (Belgium).

Poster Award winners

The 2021 winning clinical posters were presented by **Olulade Ayodele** (USA), **Nienke Biermasz** (The Netherlands), **Eleni Kourti** (France) and **Elina Peltola** (Finland). The winning basic science posters were presented by **Nathalie Boulet** (France), **David F Carregeta** (Portugal), **Salvatore Sciacchitano** (Italy) and **Vaishnavi Venugopalan** (Germany).

eECE 2021
23rd European Congress of Endocrinology



Save the date

For more information about any ESE event see www.eese-hormones.org.

ESE Young Endocrinologists and Scientists (EYES) Meeting

3–5 September 2021

Online

ESE Clinical Update on Acromegaly

13–15 September 2021

Online

ESE Spotlight on Science

16 September 2021

Online

ESE Spotlight on Science

21 October 2021

Online

EndoBridge 2021

22–24 October 2021

Online

EuroPit 2021

22–24 November 2021

Annecy, France

ESE Clinical Update on Obesity

29 November–1 December 2021

Online

ESE Spotlight on Science

2 December 2021

Online

45th Symposium on Hormones and Cell Regulation

23–26 March 2022

Mont Ste Odile, France

ECE 2022

24th European Congress of Endocrinology

21–24 May 2022

Milan, Italy

Deadlines

30 August 2021

EndoBridge Clinical Cases

Submission deadline

1 September 2021

ESE Small Meeting Grant

Application deadline

30 September 2021

45th Symposium on Hormones and Cell Regulation

Abstract submission deadline

30 November 2021

ESE Short-Term Fellowship

Application deadline