ESPE NEWS

BRINGING THE LATEST IN PAEDIATRIC ENDOCRINOLOGY TO YOU

ESPE
European Society for Paediatric Endocrinology
Improving care of children with endocrine diseases by promoting knowledge and research

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Endocrine disruptors

Their impact on the next generation
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Taking an overview

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ALSO INSIDE:

ESPE AWARDS – Make your nominations by 10 December **www.eurospe.org/awards**

Welcome

Endocrine disruptors are inescapable. We encounter them everywhere in our environment, and we are only just beginning to comprehend their effects upon our species and our fellow organisms, including future generations. The theme of this issue allows us to examine their impact in various areas of our field.

We are delighted to start with an overview of the topic by Katharina Main, who, alongside her colleagues at the Department of Growth and Reproduction at Copenhagen's Rigshospitalet, has developed great expertise in the field of endocrine disruption (**page 7**).

On **page 8**, Arno Christian Gutleb explains the situation from the perspective of thyroid hormones and development. The potential impact of thyroid hormone disruption on the developing brain should give us great cause for concern.

Stefano Cianfarani uses his article on **page 9** to discuss how exposure to endocrine disruptors during critical periods of development can permanently programme pubertal timing and long term fertility. He highlights the difficulties we face in trying to meaningfully extrapolate experimental findings from animals to humans.

Lastly, on **page 10**, Jerry Heindel contemplates how much of the obesity epidemic may result from exposure to obesogenic endocrine-disrupting chemicals. Around 50 chemicals or chemical classes have been identified which can specifically cause obesity in animal models when the exposure is *in utero*.

On a more positive note, it was a delight to see so many colleagues recently at ESPE 2019 in Vienna, Austria. As always, we are pleased to congratulate the many ESPE Award winners, and to include details and photographs on **pages 4 and 5**, along with some memories of the meeting on **page 11**. This issue is also packed with news of forthcoming application deadlines for ESPE grants (including the new ESPE Visiting Professorship), as well as the 2020 ESPE Summer School.

You will find everything you need to know inside.

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ESPE Visiting Professorship

NEW!

Application deadline 31 January 2020

'If you are interested in developing or sustaining long term international research partnerships, consider applying for an ESPE Visiting Professorship'

Faisal Ahmed, Chair, ESPE Science Committee

The ESPE Visiting Professorship supports scientific renewal and the development of long-lasting collaborations, helping established paediatric endocrinologists to develop new projects and secure funding. It is available to mid-career paediatric endocrinologists (not just professors).

Up to two recipients will be selected each year, to receive a maximum of €15 000 each to last 3 years (i.e. up to €5000 per year). The grant can be used to support multiple short visits over an extended period of time, or to host a visiting professor at the applicant's home centre.

Find out more at **www.eurospe.org/grants-awards/grants/visiting-professorship**

Apply by **31 January 2020**

New Council members

Anita Hokken-Koelega (The Netherlands) began her term as ESPE Secretary General at the recent Annual Business Meeting. We also welcomed the following new members to Council:

Nils Krone (UK) Programme Organising Committee Chair

Michel Polak (France) Corporate Liaison Board Chair

Rasha Hamza (Egypt) Education and Training Committee Chair

In addition, **Evangelia Charmandari** (Greece) was re-elected as Clinical Practice Committee Chair. **Anders Juul** (Denmark) joined Council as President-Elect. We look forward to working with them all.

A call for nominations for Council vacancies in 2020 will be issued in December.

ESPE e-Learning news

www.espe-elearning.org

Registration is **free!**

New items under 'General Content'

Under 'Thyroid Disorders' we have a new case: 'A 5-year-old boy with prominent lips and sessile papules on the tongue'

Under 'Calcium and Bone' there is a new chapter and a case, both entitled: 'Metabolic bone disease of prematurity'

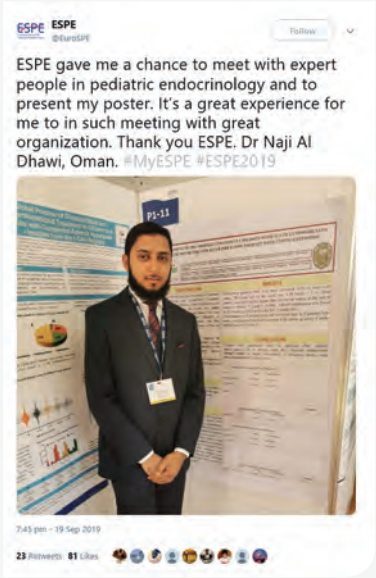
New items under 'Resource Limited Countries'

The 'Resource Limited Countries' module has been completed. It offers 16 chapters and 24 cases in English, French, Spanish, Swahili and Chinese

'My photo – my ESPE'

Delegates at ESPE 2019 in Vienna had the chance to win a year of free ESPE membership, by tweeting a photo of themselves during the meeting and saying what ESPE means to them.

The author of the message that received most likes when it was retweeted from @EuroSPE was **Naji Al Dhawi** from Oman, whose Tweet (pictured) received 79 likes by the deadline. Congratulations Naji!



ESPE Meeting 2024

Following a ballot, we are pleased to announce that the 2024 Annual Meeting of ESPE will take place in Marseille, France, with Rachel Reynaud as President.

Early Career Scientific Development Grant

This grant can be used to support a short visit to an external laboratory, hospital or institute to gather information and experience regarding a specific research issue or laboratory technique.

Alternatively, it could finance the visit of an external expert to provide guidance, consultation or advice at your home institute.

Four grants of up to €2500 each are available annually.

Find out more at **www.eurospe.org/grants-awards/grants/early-career-scientific-development-grant**

The next deadline is **31 January 2020**

ESPE-IFCAH Grants 2020

ESPE is pleased to support IFCAH (the International Fund for Congenital Adrenal Hyperplasia). This private fundraising organisation aims to promote academic research in the field, to improve understanding and management of CAH.

ESPE-IFCAH Grants totalling €350 000 will be available in 2020, with selected research projects receiving up to €150 000.

Find out more at **www.eurospe.org/grants-awards/grants/ifcah-espe-grant**

Submit letters of intent by **15 January 2020**

ESPE Research Unit Grant

The ESPE Research Unit Grant supports collaborative high quality research in paediatric endocrinology, for both physicians and scientists. Visit **https://youtu.be/BzsIFQrL_Lw** to hear what this grant meant for 2016 recipient Magdalena Stefanija Avbel (Slovenia), and then make sure you apply by the forthcoming deadline.

Find out more at **www.eurospe.org/grants-awards/grants/research-unit**

Deadline **28 February 2020**

ESPE Award Winners 2019

We congratulate the winners of the 2019 ESPE Awards, many of whom received their prizes at the ESPE Meeting in Vienna, Austria, in September.

ESPE Andrea Prader Prize

Jesús Argente (Madrid, Spain) received the ESPE Andrea Prader Prize, in recognition of his lifetime achievement in teaching and research, outstanding leadership and overall contribution to the field of paediatric endocrinology.

ESPE Outstanding Clinician Award

Jan Lebl (Prague, Czech Republic) was presented with the ESPE Outstanding Clinician Award, in recognition of his outstanding clinical contribution to the practice of paediatric endocrinology.

ESPE International Award

Maria New (New York, USA) received the ESPE International Award. This is presented to an outstanding paediatric endocrinologist from a country outside Europe and the Mediterranean basin.

ESPE International Outstanding Clinician Award

Abiola Oduwole (Lagos, Nigeria) received the ESPE International Outstanding Clinician Award, in recognition of her contribution and commitment to clinical paediatric endocrinology in a country outside Europe and the Mediterranean basin.

ESPE Research Award

Irène Netchine (Paris, France) received the ESPE Research Award, in recognition of research achievements of outstanding quality in basic endocrine science or clinical paediatric endocrinology.

ESPE Young Investigator Award

Sabine

This award is for paediatricians who are still in training or have had no more than 5 years in a senior (principal investigator) role, in recognition of their scientific publications. It was presented to **Sabine Hannema** (Leiden, The Netherlands), whose award lecture was entitled 'Endocrine care for transgender adolescents'.

Henning Andersen Prizes

Anu

Philippe

These awards for the most highly rated abstracts were presented to:

- **Anu Bashamboo** (Paris, France) for 'Development of testicular organoids to understand disorders of sex development'
- **Philippe Lysy** (Brussels, Belgium) for 'Partial CRISPR/Cas9 IL1R1 and IFNGR1 knock-down improves β-cell survival and function under cytokine-induced inflammation'.

President's Poster Awards

(L-R) Lana, Sophie, Susanne and Sari, with ESPE 2019 President Gabriele Häusler (centre)

This year's prizes for the best posters at the meeting were awarded for the following abstracts:

- 'Hypothalamus and pituitary gland antibodies in childhood-onset brain tumors and pituitary dysfunction' by **Giuseppa Patti** *et al.* (Italy)
- 'Establishing a novel NGS tool for the diagnosis of X-linked hypophosphatemia (XLH)' by **Susanne Thiele** *et al.* (Germany)
- 'Empagliflozin and GABA improve β-cell mass and glucose tolerance in new-onset type 1 diabetes' by **Caroline Daems** *et al.* (Belgium), poster presented by **Sophie Welsch**
- 'The first description of large pathogenic deletion in *ACAN* gene and additional cases with novel pathogenic *ACAN* variants' by **Lana Stavber** *et al.* (Slovenia)
- 'Factors associated with dyslipidemia in patients with type 1 diabetes: a single-center experience' by **Sari Krepel Volsky** *et al.* (Israel).

ESPE Research Fellowship

Patrick Hanna (Paris, France) has been awarded this fellowship, which enables talented young scientists, investigators and paediatric endocrinologists to conduct research at leading institutions worldwide, for 'GNAS mutations and epimutations: deciphering the molecular mechanisms' at the Endocrine Unit at Massachusetts General Hospital, Boston, USA (€140 000).

ESPE Research Unit Grant

Awards have been made to the following recipients, to facilitate collaborative research in paediatric endocrinology:

- **Adalbert Raimann** (Vienna, Austria) for 'ViD-MeX: pilot study on vitamin D metabolism in X-linked hypophosphatemic rickets (XLH)' (€15 000)
- **Guiomar de Nanclares** (Vitoria-Gasteiz, Spain) for 'New clinical and molecular findings in patients with inactivating PTH/PTHrP signalling disorders' (€130 000).

ESPE *Hormone Research in Paediatrics* Prizes

These prizes for the best original papers published in *Hormone Research in Paediatrics* were presented to:

- **Walter Bonfig** *et al.* (Germany/Austria) for 'Sodium chloride supplementation is not routinely performed in the majority of German and Austrian infants with classic salt-wasting congenital adrenal hyperplasia and has no effect on linear growth and hydrocortisone or fludrocortisone dose' *Hormone Research in Paediatrics* **89** 7–12 (best original paper)
- **Vrinda Saraff** *et al.* (UK/France) for 'Continuous subcutaneous recombinant parathyroid hormone (1–34) infusion in the management of childhood hypoparathyroidism associated with malabsorption' *Hormone Research in Paediatrics* **89** 271–277 (best 'Novel Insights from Clinical Practice' paper).

IFCAH-ESPE Grants

These awards were presented for research into congenital adrenal hyperplasia (CAH):

- **Nicole Reisch & Richard Auchus** (Munich, Germany) for 'Prospective long term follow-up of hypothalamus-pituitary-gonadal (HPG) axis in males with CAH' (€100 000)
- **Claudia Boettcher** (Muri bei Bern, Switzerland) for 'Oral contraceptives in female adolescents with CAH: impact on the metabolome, and a way to optimize treatment with respect to androgen excess?' (€75 000)
- **Anna Nordenström** (Stockholm, Sweden) for 'Effects and importance of adrenalin deficiency in CAH' (€75 000).

ESPE Clinical Fellowship

These fellowships to promote patient care, clinical management and clinical research in paediatric endocrinology have been awarded to **Ugo Chikani** (Nigeria), **Chetankumar Dave** (India), **Farel Elilie Mawa Ongoth** (Congo), **Diana-Alexandra Ertl** (Austria), **Gunay Jabrayilova** (Azerbaijan), **Dhivyalakshmi Jeevarathnam** (India), **Ioannis Kyrgios** (Greece), **Nikhil Lohiya** (India), **Fozia Memon** (Pakistan), **Diana Miclea** (Romania), **Ourida Nasma Taleb** (Algeria), **Lusine Navasardyan** (Armenia), **Sapna Nayak** (India), **Kiran Pabri** (India) and **Doğuş Vurallı Karaoğlan** (Turkey).

Bringing you recent highlights from the world of research

Exocrine or endocrine? A pancreatic elastase in metabolic syndrome

Using next-generation sequencing in patients with metabolic syndrome and early onset atherosclerosis, Esteghamat *et al*. have identified *CELA2A* (chymotrypsin-like elastase family member 2A) as a candidate gene for metabolic syndrome and increased risk for cardiovascular disease.

The CELA2A enzyme is secreted by the acinar cells of the exocrine pancreas into the gut and into the circulation to break down proteins. In the circulation, CELA2A enhances insulin degradation but, most importantly, it also reaches the pancreatic islets and upregulates insulin secretion by activating calcium channels in β cells. This observation is fascinating, because the exocrine and endocrine pancreas were considered to be functionally unconnected, despite their intimate physical connection and shared embryological origin.

Last, but not least, CELA2A cleaves integrin A2B, a component of a receptor complex that binds fibrinogen and triggers platelet aggregation, and therefore mutations in *CELA2A* lead to increased risk of atherosclerosis.

Read the full article at Esteghamat *et al*. 2019 *Nature Genetics* 51 1233–1243, with a commentary at Gloyn 2019 *Nature Metabolism* 1 853–855

Iodine fortification and thyrotoxicosis

Petersen *et al.* identified and scrutinised all possible new cases of overt thyrotoxicosis and hypothyroidism occurring during 2014–2016 in an open cohort in Northern Jutland, Denmark (*n*=309 434). This region was first studied using an identical survey in 1997–2000, prior to mandatory iodine fortification of salt, which happened in Denmark in 2001.

The standardised incidence rate (SIR) of verified overt thyrotoxicosis decreased markedly, from 97.5/100 000 per year in 1997–2000, to 48.8 in 2014–2016 (SIRR: 0.50; 95% CI: 0.45–0.56). This remarkable reduction was due to a substantial decrease in the SIR of multinodular toxic goitre (SIRR: 0.18; 95% CI: 0.15–0.23), solitary toxic adenoma (SIRR: 0.26; 95% CI: 0.16–0.43) and, to a lesser degree, Graves' disease (SIRR: 0.67; 95% CI: 0.56–0.79). By contrast, there was no significant change in the overall incidence of verified hypothyroidism (SIRR: 1.03; 95% CI: 0.87–1.22).

These data show a 50% reduction in thyrotoxicosis incidence after 15 years of mandatory salt iodisation, with no significant increase in overt hypothyroidism.

Read the full article at Petersen *et al*. 2019 *Clinical Endocrinology* doi: 10.1111/cen.14072

Efficacy and safety of asfotase alfa in hypophosphatasia

Hypophosphatasia (HPP) is a rare inherited disease characterised by low activity of the tissue-non-specific isoenzyme of alkaline phosphatase, leading to extracellular accumulation of its substrates.

To evaluate the efficacy and safety of asfotase alfa in patients aged <5 years with HPP, Hofmann *et al.* conducted a phase 2 open-label study across 22 sites and 12 countries, with a follow-up period of 6 years. In total, 69 patients with onset of severe HPP before the age of 6 months were chosen. The primary efficacy measure was radiographic global impression of change score (RGI-C). During median 2.3 years of treatment, RGI-C scores improved significantly at month 6, year 1 and last assessment (P<0.0001). Of 24 patients requiring respiratory support at baseline, 11 no longer needed support. Height/weight z scores generally increased.

Thus, asfotase alfa may be a promising therapy for children with HPP-related skeletal manifestations and impairment of respiratory function and growth.

Read the full article at Hofmann *et al*. 2019 *Journal of Clinical Endocrinology & Metabolism* 104 2735–2747

Benefits of GH/GnRHa in increasing adult height in ISS

Outcomes of growth hormone (GH) therapy in idiopathic short stature (ISS) are variable, due to the heterogeneous cohort. GH treatment is particularly challenging in cases with early onset of puberty or who are pubertal at GH start.

Lazar *et al.* undertook a retrospective observational study of 192 children with ISS, of whom 70% received GH alone and 30% received combined GH and GnRH analogue (GnRHa). The combined treatment was more common in those who were already pubertal at initiation of therapy and in girls.

At onset of puberty, children treated with combined GH/GnRHa were younger and their predicted adult height was shorter than those treated with GH alone. The average duration of GnRHa treatment was 2 years and the GH dose was standardised at 0.05mg/kg per day.

At final height analysis, prepubertal status at initiation of GH therapy predicted the best height outcomes, with prepubertal status and combined GH/GnRHa therapy predicting a final height better than the target height. Combined GH/GnRHa significantly increased adult height versus predicted adult height and versus target height.

GnRHa therapy should be considered in ISS children on GH treatment who are pubertal at GH initiation or who have early pubertal development.

Read the full article at Lazar *et al*. 2019 *Journal of Clinical Endocrinology & Metabolism* 104 3287–3295

Endocrine disruption: an overview

Research has spanned three decades, but much remains to be learnt, as Katharina Main explains.

Katharina Main (right), with colleagues Anders Juul and Anna-Maria Andersson

> *"The total human exposure to EDCs is virtually unknown and most likely underestimated"*

Several non-communicable diseases are increasing in number worldwide. These include a broad range of reproductive, endocrine, metabolic, immunological and neurological disorders, as well as certain cancers. Semen quality has decreased in several Western countries, and an increasing number of young people experience fertility problems which cannot be explained by advanced maternal age alone. At the same time, the incidence of testicular cancer has risen in many countries, as has the prevalence of cryptorchidism and hypospadias in newborn boys.

Discoveries of the last 30 years

The increase in male reproductive disorders has occurred over a relatively short time span, indicating that environmental factors and modern lifestyle may play a role.

In 1991, Niels Erik Skakkebæk organized a WHO workshop in Copenhagen, Denmark, on the impact of the environment on reproductive health. One paper at the meeting presented evidence that industrial chemicals to which populations were exposed could have oestrogenic effects. Another study showed that male reproductive health was deteriorating among normal men. These new data led to the idea that there might be an association between the exposures, semen quality and testicular cancer.[1]

Soon after the WHO meeting, the 'oestrogen hypothesis' was published.[2] It was intensely debated and even disputed in scientific and public domains, but the past two to three decades of research have shown that all endocrine systems can be negatively affected by endocrine-disrupting chemicals (EDCs): for example, the thyroid, pituitary, testes, ovaries and pancreas. Some EDCs may even act on several systems simultaneously.

The fetus appears particularly susceptible to endocrine-disrupting effects, with life-long health consequences,[3,4] some of which may even be heritable, due to epigenetic alterations.

An incalculable cost

Conservative estimates of health costs related to male reproductive disorders in Europe reach €130 million and €848 million respectively for cryptorchidism and testicular cancer related to polybrominated diphenyl ether (PBDE) exposure. For phthalate-related decreases in testosterone in men and infertility treatment, the respective amounts are as much as €7.96 billion and €4.71 billion.[5]

An immeasurable problem

Since the turn of the nineteenth century, tens of thousands of manmade chemicals have entered our lives, and we are all exposed to thousands of these chemicals and their degradation products. Most of these compounds and their metabolites have never been tested for endocrine effects. Thus, the total human exposure to EDCs is virtually unknown and most likely underestimated.[6]

Even for some chemicals already known to be EDCs, human exposure data are often limited, mainly due to lack of specific analytical methods and the high analytical cost involved.

Although adverse health effects may be caused by single compounds, animal studies unequivocally show that different chemicals interfering with the same endocrine system often show dose-additive effects. Our knowledge about mixture effects in humans and how mixtures interact with lifestyle factors, such as a sedentary lifestyle, high fat food, smoking or alcohol, is still very limited. Targeted analysis of individual chemicals tends to be aimed at 'the usual suspects' and we may lack crucial information on important compounds simply because we do not look for them.

An urgent need to address

Several academic societies, e.g. ESPE, the European Society of Endocrinology, the Endocrine Society and the International Federation of Gynecology and Obstetrics, have published statements saying that exposure to these chemicals is a considerable health threat which we urgently need to address. Societies have also initiated networks of dedicated scientists to promote research, share knowledge internationally and influence decision makers within public authorities and local governments, to encourage a precautionary principle in choices for future generations.

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References
1. Michal *et al.* 1993 *Environmental Health Perspectives* **101** Suppl 2 159–167.
2. Sharpe & Skakkebæk 1993 *Lancet* **341** 1391–1395.
3. Skakkebæk *et al.* 2001 *Human Reproduction* **16** 972–978.
4. Juul *et al.* 2014 *Nature Reviews Endocrinology* **10** 553–562.
5. Hauser *et al.* 2015 *Journal of Clinical Endocrinology & Metabolism* **100** 1267–1277.
6. Skakkebæk *et al.* 2016 *Physiological Reviews* **96** 55–97.

Thyroid hormone disruption and development

Plasma thyroid hormone disruptor levels fall well within the range of reported effect concentrations, with serious implications, as Arno Christian Gutleb describes.

Arno Christian Gutleb

The thyroid hormone system

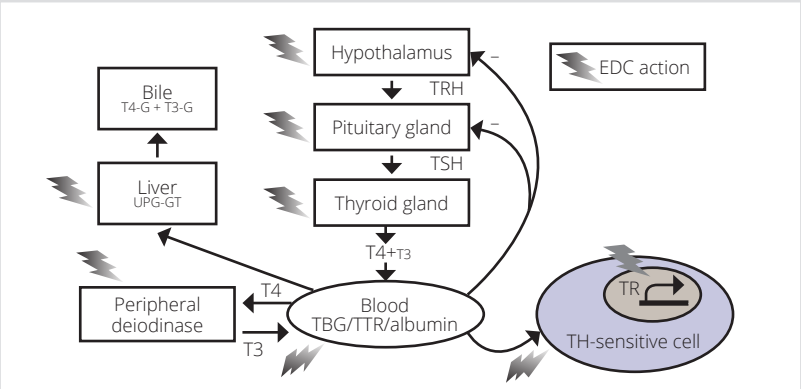
The thyroid hormone (TH) system is very important for central physiological processes in humans, encompassing growth and cell differentiation, energy metabolism, brain development, reproduction and the cardiovascular system.

Several chemicals are known to be TH-disrupting compounds (THDCs), and these have been shown to interact with almost every element of TH homeostasis, including feedback mechanisms with the hypothalamo-pituitary axis, TH synthesis, TH storage and release from the thyroid gland, transport protein binding and TH distribution in tissues and organs, cellular TH uptake, intracellular TH metabolism, and TH receptor binding (Figure).

This is of great relevance, as reported plasma concentrations of THDCs in humans fall well within the range of reported effect concentrations, and this is even more true for the developing fetus and young children, who are at sensitive developmental stages.

Generally, decreased TH levels during pregnancy can result in serious alteration of the neurodevelopment of the developing fetus. Therefore, mandatory screening for thyroid function in pregnant women is a standard procedure in many countries. Overall, the potential effects of chemicals interfering with TH homeostasis need careful attention.

> *Evidence from epidemiological studies of a relationship between exposure to THDCs and brain developmental disorders is increasing"*



Points at which endocrine-disrupting chemicals (EDCs) have been shown to interfere with the thyroid hormone (TH) system. T3, tri-iodothyronine; T3-G, glucuronosyl T3; T4, thyroxine; T4-G, glucuronosyl T4; TBG, thyroxine-binding globulin; TR, thyroid hormone receptor; TRH, thyrotrophin-releasing hormone; TSH, thyrotrophin; TTR, transthyretin; UDP-GT, UDP-glucuronosyltransferase

Interference with THs

Transport of THs in mammals is mainly dependent on thyroxine-binding globulin or transthyretin (TTR). TTR is synthesised in the liver and the brain and is involved in the transport of thyroxine across the blood–brain barrier and maternal–fetal transport through the placenta.

Many hydroxylated metabolites of persistent organic pollutants (such as hydroxylated polychlorinated biphenyl (OH-PCB) metabolites) show high binding affinity for TTR, which can exceed that of thyroxine. The resulting effect *in vivo* is the retention of these compounds in the plasma, facilitating their transport through the placenta and enrichment in the fetal compartment, with decreased maternal and fetal plasma thyroxine. Importantly, OH-PCBs have been found in humans and wildlife at high levels exceeding *in vitro* and *in vivo* effect concentrations.

Low THs and developing brain

THs are essential for many aspects of brain development during gestation and early in childhood. Any disturbance of the delicate balance of THs with respect to local concentrations may lead to life-long effects, either by inducing organisational changes or by altering set points.

The developing fetus depends strongly on maternal TH provided via the placenta in the first trimester. Early fetal TH insufficiency contributes to alterations of the hippocampus, observable as anatomical changes and resulting in suboptimal performance in memory tasks. TH signalling is present during early embryogenesis; this is the critical window, with high vulnerability to disruption of TH. Alterations of TH due to lack of iodine, maternal hypothyroidism, TH transport disturbance and alterations of peripheral TH metabolism may result in permanent alterations of neuronal development.

Evidence from epidemiological studies of a relationship between exposure to THDCs and brain developmental disorders is increasing. Concentrations of PCB metabolites in cord blood have shown a significant association with a reduced mental development index. THDC exposure is likely to be linked with the observed increase in autism spectrum disorder symptoms or IQ loss.

In conclusion

The costs of neurodevelopmental disability and associated costs related to endocrine-disrupting chemical exposure in the EU were recently calculated to be €150 billion per year, when taking into consideration direct costs such as treatment and indirect costs such as loss of productivity. This health issue is too important to be overlooked, especially as humans are still exposed to such chemicals at levels above the *in vitro* and *in vivo* effect concentrations.

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Further reading
Gutleb *et al.* 2016 *Hormone Research in Paediatrics* **86** 271–278.

Endocrine disruptors and pubertal timing

Stefano Cianfarani considers the complex effects of environmental factors on the timing of puberty.

Definition and implications

The European Commission's current definition of an endocrine disruptor (ED) is 'an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations'. This includes a broad range of effects potentially affecting all endocrine functions. EDs interfere with the endocrine physiology at multiple target sites, from hormone secretion and transport to receptor binding and signalling.

Although genetic factors account for 50–80% of the variance of age at puberty, the impact of environmental factors on pubertal timing has recently been proposed. The sensitivity to environmental cues is particularly high in specific critical periods characterised by biological plasticity, which ensures that the organism assumes the appropriate features to match the surrounding environment. Fetal and early postnatal life are classically considered the time windows with the maximum adaptation capacity. Exposure to adverse environmental cues, such as EDs, during critical periods of development can permanently programme pubertal timing and long term fertility.

Stefano Cianfarani

> *"Exposure to adverse environmental cues during critical periods of development can permanently programme pubertal timing and long term fertility"*

Evidence in animals

Several animal studies suggest that environmental factors may interfere with pubertal timing by inducing biochemical, genetic and epigenetic changes. There is robust evidence in animals showing a close relationship between alterations of puberty and exposure to EDs, such as dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), bisphenol A (BPA), phthalates, polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs). Most EDs act as oestrogen and androgen agonists or antagonists, ultimately leading to a central (neuroendocrine) or peripheral disruption of the hypothalamus-pituitary-gonadal axis.

The results obtained in animals are, however, conflicting, showing normal, early and late initiation of puberty induced by the same ED in the same species. Furthermore, the findings from animal models can hardly be applied to humans, as the dynamics of puberty is species-specific and experimental data are obtained from exposure to one single ED. This is not the case in humans, who are exposed to a mixture containing multiple EDs at the same time.

Evidence in humans

The report on the consequences of the accidental contamination of the Michigan food chain with polybrominated biphenyls (PBBs) in 1973 was a milestone in understanding the epidemiology of ED effects in human beings. In this report, an earlier age at menarche was observed in breastfed girls exposed to high levels of PBB *in utero*.

Other observational studies have often, but not always, confirmed the association between exposure to EDs and alterations in pubertal timing. For instance, an outbreak of premature thelarche and ovarian cysts in Puerto Rico (1990–1995) was associated with exposure to phthalates and brominated flame retardants. Higher urinary concentrations of 2,5-dichlorophenol were associated with an earlier onset of menarche (by 7 months), whereas urinary levels of mono-3-carboxypropyl phthalate (MCPP) were associated with a 4- to 5-month greater age at both thelarche and menarche in a cohort of 1051 girls followed longitudinally.

A number of case–control studies have been conducted, yielding conflicting results. Higher serum concentrations of PBDE have been reported in girls with premature thelarche but not in girls with precocious puberty. Overall, the prevailing opinion, stemming from early observational studies, is that exposure to EDs induces an advancement in female pubertal timing. However, recent evidence indicates that both boys and girls may experience alterations in pubertal timing, with early initiation but delayed completion of puberty.

Conclusions

Although EDs may interfere with several biological processes, including puberty, a number of factors affect the interpretation of data.

(1) Each individual is exposed to many different EDs from conception to old age and always to a mixture rather than to a single substance.
(2) The effects are often not dose-dependent and even exposure to 'negligible' doses of chemicals may be disrupting.
(3) The effects are species-specific, making it impossible to reliably infer the biological consequences from observations of what occurs in wildlife to human beings.
(4) Effects are age- and sex-dependent.
(5) EDs may have transgenerational effects, probably due to epigenetic changes that transmit ED effects to subsequent generations even in the absence of direct exposure.

Stefano Cianfarani
Bambino Gesù Children's Hospital, Tor Vergata University, *Rome, Italy,* **and Karolinska Institutet and University Hospital,** *Stockholm, Sweden*

Obesogens and obesity

Jerry Heindel contemplates how much of the obesity epidemic results from exposure to obesogenic endocrine-disrupting chemicals.

Jerry Heindel

> *We know of about 50 chemicals or chemical classes that can specifically cause obesity in animal models when the exposure is* in utero"

We are experiencing a global obesity pandemic that impacts everyone, including infants and children.[1] The prevailing theory is that this pandemic results from overnutrition (more food choices, easy access to foods, more high fat and high sugar foods) and insufficient exercise. While improving nutrition and increasing exercise are good ideas, this approach to reducing obesity is not working; the pandemic continues to grow despite a myriad of diets and exercise programmes.

So what is missing? Obesity is a complex, multifactorial endocrine disease that is also strongly influenced by the microbiome, genetics, drugs, viruses, infections, smoking during pregnancy and endocrine-disrupting chemicals (EDCs).

The Endocrine Society defines EDCs as exogenous chemicals or mixtures of chemicals that can interfere with any aspect of hormone action.[2] About 1000 environmental chemicals have been characterised as EDCs. Exposure occurs via food, water, air and skin. EDCs are ubiquitous; each of us is exposed to a variety of EDCs, albeit at differing concentrations and times.[3]

A developmental origin

Like most non-communicable diseases, obesity has its origins during development. The endocrine system is critical to controlling energy balance, fat development, deposition and distribution, and eating behaviours. Hormones and growth factors integrate control of the development of the brain, adipose tissue, gastrointestinal tract, muscle, liver and pancreas *in utero*. This finely orchestrated system can be disrupted by EDCs, leading to the 'wrong hormone' or the 'right hormone' but at the wrong time, place or levels.

Disruption of endocrine control by EDCs can result in permanent disturbances at the molecular level, with altered gene expression and disrupted metabolic pathways, which can result in increased susceptibility to weight gain later in life.

We know of about 50 chemicals or chemical classes that can specifically cause obesity in animal models when the exposure is *in utero*.[4] These EDCs are called obesogens or metabolism disruptors.[5] Many of these same chemicals have been associated with weight gain in children and adults in human birth cohort studies.[6]

The impact of EDCs

A key question is how much of the obesity epidemic results from exposure to obesogenic EDCs? Of course, there is no clear answer to that question, just as there is no easy way to determine what fraction of obesity is genetic, or due to stress, changes in the microbiome or overeating. The reason is simple: all these factors interact, affecting multiple pathways that can result in obesity.

Importantly, we can show in animal models that exposure to obesogens can lead to changes that mimic the human situation. For example, obesogens can:

(a) increase the number of neurones in the brain that control appetite, leading to overeating
(b) decrease metabolic rate, making it easier to gain weight
(c) reduce energy expenditure, leading to weight gain
(d) sensitise the body to weight gain on a high fat diet, and
(e) produce dysfunctional adipocytes that have an impaired ability to mobilise fat.

Obesogens can also make it harder to lose weight and easier to gain weight on the same diet. Some obesogen effects are sexually dimorphic, again mimicking the human situation.

What is the solution?

While it is essential to continue dietary modification programmes and increase exercise, these interventions are unlikely to be fully successful without considering all the factors contributing to weight gain, including exposure to obesogens.

The contribution of obesogens to the obesity epidemic can be diminished by reducing exposures to these chemicals, particularly *in utero* and during early childhood, as well as undertaking behavioural changes and other interventions that can reduce the effects of prior exposures on metabolism.[7,8]

Since programming of adipocyte development and control of metabolism continues beyond the *in utero* situation well into infancy and childhood, there is an important role for the paediatric community in reducing the obesity epidemic. By educating patients about the importance of reducing exposures to obesogens, they may reduce susceptibility to weight gain later in life.

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Commonweal's Healthy Environment and Endocrine Disruptor Strategies is a non-profit multidisciplinary coalition of scientists dedicated to improving communication, co-ordination and collaboration in the field of endocrine disruption (see ***www.heeds.org****).*

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