



RESEARCH UPDATE:

Paediatric and Adolescent Gynaecology

Here, ESPE Paediatric and Adolescent Gynaecology (PAG) Working Group Co-ordinator Lourdes Ibáñez brings you up to date with recent advances in the field, in the first of our regular research updates.

Late effects of cancer therapy

An increasing number of girls and young women with cancer survive and have to endure the long term consequences of chemotherapy, such as premature ovarian failure and infertility. The field of fertility preservation and/or restoration, as well as the management of premature ovarian failure after gonadotoxic treatments, have significantly progressed, opening new perspectives.

Polycystic ovary syndrome

Hyperinsulinaemic androgen excess, namely polycystic ovary syndrome (PCOS), is the most common cause of hirsutism, acne and menstrual irregularity in adolescent girls. Recently, it has been suggested that the disorder frequently originates from an absolute or relative excess of lipids in adipose tissue, and from associated changes in insulin sensitivity, gonadotrophin secretion and ovarian androgen release. Accordingly, although lifestyle intervention is essential to reduce adiposity in obese girls, in those without obesity who are not sexually active, insulin sensitisation has proved to have more normalising effects than oestradiol-progestogen combinations.

Genes and environment in puberty

Studies of the role of genetic and environmental factors in pubertal development and beyond have experienced a significant leap recently, as judged by the publications discussed below.

Circulating MKRN3 levels decline prior to pubertal onset and through puberty

Hagen *et al.* 2015 *Journal of Clinical Endocrinology & Metabolism* Feb 19;jc20144462

[Epub ahead of print]

The authors provide further evidence that makorin RING-finger protein 3 (MKRN3) – an intronless gene located on chromosome 15q11.2 in the Prader-Willi syndrome critical region – is a major regulator of hypothalamic gonadotrophin-releasing hormone secretion during childhood. Abreu and colleagues first described mutations in MKRN3 as a cause of familial central precocious

ESPE News Contents (click on a link below)

- ⊗ ESPE update
- ⊗ Register today for ESPE 2015
- ⊗ ESPE e-Learning news
- ⊗ ESPE 2015: speakers' previews
- ⊗ ESPE award winner: Jean-Pierre Bourguignon
- ⊗ ESPE award winners: Moshe Phillip and Oliver Semler
- ⊗ Hans Helge (1935-2015)
- ⊗ *Yearbook of Pediatric Endocrinology*: Editor's preview
- ⊗ Dutch Society for Paediatrics - Endocrinology Section
- ⊗ Future meetings and deadlines

ESPE Newsletter survey

Please tell us what you think!

Complete a short survey [HERE](#)

Welcome to issue 28

DEAR FRIENDS AND COLLEAGUES,
Thank you to everyone who has completed our newsletter survey so far. Your feedback is extremely useful to us. We are keeping the survey open for one more issue only, so if you have not had your say please complete it now. It only has a few questions and really will only take 2 minutes of your time. We will share the results with you at a later date.

This issue brings you the first in an exciting series of new 'Research Updates', where the ESPE Working Groups take turns to summarise the latest news from their relevant field. On this page, Lourdes Ibáñez brings you a report from the Paediatric and Adolescent Gynaecology Working Group. We hope you will enjoy this Research Update and continue to enjoy them in future issues.

The abstract deadline for the 54th Annual Meeting of ESPE in Barcelona has already



54th Annual Meeting 1-3 October
ESPE 2015 BARCELONA
European Society for Paediatric Endocrinology

[Read more on page 2](#)

Don't forget! Early bird registration deadline: **8 June 2015**

www.espe2015.org

Welcome *continued from page 1*

passed, and soon the early bird registration deadline will be upon us (8 June). Below, Laura Audí updates us on preparations for the event, while on [page 4](#), you can find previews of some of the key lectures, to whet your appetite. This is a meeting you can't afford to miss!

You are sure to be inspired by the stories of medal winners from ESPE 2014, as Andrea Prader Prize recipient Jean-Pierre Bourguignon, Research Award recipient Moshe Phillip and Young Investigator Award recipient Oliver Semler share their experiences with us on [pages 5–6](#). We thank them all for their contributions.

It is with sadness that we report the death of Hans Helge, pioneer of paediatric endocrinology. On [page 7](#), you can read a tribute to his hugely productive career.

Other news includes the regular update from the ESPE Team (below), an update on the e-Learning Programme ([page 3](#)), and the latest activities of the Endocrinology Section of the Dutch Society for Paediatrics ([page 8](#)). On [page 8](#), we are also delighted to include an excerpt from the *Yearbook of Pediatric Endocrinology* from Ken Ong.

I would also like to thank Lars Sävendahl for his continuous support and all my colleagues in the Newsletter team for their assistance with this issue, which is greatly appreciated.

Yours sincerely,
Professor Feyza Darendeliler
Editor, ESPE Newsletter
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EDITORIAL BOARD

Indi Banerjee, Manchester, UK
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IT'S BEEN A BUSY SPRING. The Winter and Diabetes/Obesity Schools have both taken place, with great feedback from the attendees. You can find our full programme for 2015 at www.eurospe.org.

In March we attended the ESPE Council meeting in Prague; at www.facebook.com/EuroSPE you'll see the Council members and ESPE team on location. The meeting's theme was 'the future of ESPE', and Council devoted a full extra day to considering ESPE's strategy and activities.

Would you like to get more involved with ESPE? Vacancies on our committees occur regularly and are advertised in your monthly news alerts, so please watch out. We are particularly keen to see younger members more widely represented. Being on a

ESPE update

committee is a great way to get your ideas heard, see them develop and get to know more of your colleagues across Europe.

We are also busy gearing up for Barcelona and look forward to seeing many of you there at the ESPE Connect Stand. Have you arranged your accommodation yet? Hotels are already filling up, so, if you haven't already, we recommend booking soon to get your preferred choice. See www.espe2015.org/accommodation.

Did you know there are significant ESPE membership discounts for fellows-in-training, nurses and allied health care professionals, as well as those from low and middle income countries? If your colleagues would benefit from these, please spread the word and encourage them to think about joining our Society. Find out more at www.eurospe.org/membership.

Finally, remember to look out for your monthly news alert email, with all the important dates and deadlines for ESPE events and activities. And don't forget to join us on Facebook (www.facebook.com/EuroSPE) and Twitter (www.twitter.com/eurospe) for the latest information.

Joanne Fox-Evans, Lucy Lawrance and Tracey-Leigh Meadowcroft, ESPE Team

Register today for ESPE 2015



54th Annual Meeting 1-3 October
ESPE 2015 BARCELONA
European Society for Paediatric Endocrinology

DEAR FRIENDS AND COLLEAGUES,

I hope that you have had a successful and enjoyable spring! 2015 has already seen some great things for ESPE and there are many more to come, such as the 54th ESPE Annual Meeting in Barcelona on 1–3 October.

Together with the ESPE Council, Programme and Local Organising Committees and Bioscientifica, as well as the contribution of the Barcelona Convention Bureau and the support of ESPE Platinum and Gold Sponsors, we are working to bring you an excellent, exciting and fruitful 2015 meeting.

Speakers are now being confirmed and the programme as a whole is taking shape wonderfully. In addition to the six plenary lecturers, the ESPE 2015 meeting will welcome speakers from across the world, delivering a comprehensive programme of workshops, educational symposia, and Meet the Expert and free communication sessions. You can find a flavour of some of the talks on [page 4](#).

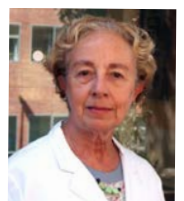
All abstracts for oral and poster communications have now been received and there have been some great submissions. Late-breaking abstracts will still be considered; submission will be open from Monday 8 June until Monday 6 July.

Make your way to the website now at www.espe2015.org, where you will find all the information you need about the scientific programme, late-breaking abstract submission, registration, hotels and the city of Barcelona.

With the event now less than 5 months away, it is the ideal time to register. Early bird registration is available until 8 June and could save you over €100!

I encourage you to register today at www.espe2015.org!

My best wishes,
Dr Laura Audí
ESPE President 2015



ESPE e-Learning news



www.espe-elearning.org

THE ESPE E-LEARNING PORTAL supports the development of competencies and skills at two levels: core (medical students) and advanced (fellows/postdocs). ESPE members can access the portal's general learning content through the members' area of the ESPE website. It is also freely available to non-ESPE members worldwide by logging into www.espe-elearning.org.

The portal provides up to date chapters and problem-solving cases on growth, puberty, disorders of sex development (DSD), calcium and bone, diabetes, hyperinsulinism, thyroid and adrenal. Several chapters and cases have been newly released online, as follows.

DSD

- Chapter: Normal and abnormal gonadal development (Leendert Looijenga *et al.*)

Growth

- Four cases of extreme short stature (Cecilia Camacho-Hubner)
- Case study: why am I so short? (Stenvert Drop)
- Case study: Yu Ting a boy with leukaemia (Wilma Oostdijk)
- Chapter: Tall stature (Stenvert Drop)

Hyperinsulinism

- Chapter: Hyperinsulinism (Evelien Gevers *et al.*)

Adrenal

- Chapter: Adrenal (Hedi Claahsen-van der Grinten)

Other developments include the option to construct specific courses for an event or organisation, as well as a set of question types allowing scoring and assessment of competencies.



During ESPE 2014 last September, we demonstrated the interactive presentation of a case by a tutor in a classroom or lecture hall situation (pictured). The case history and questions were beamed onto the screen and presented by the teacher. The audience was invited to vote for multiple choice answers using their own mobile device (phone/tablet). The audience's reply was then shown on the screen, leading to further discussion.

We are grateful for the contributions of the review board: Sarah Ehtisham (Manchester, UK), Danielle van der Kaaij (Toronto, Canada), Loredana Marcovecchio (Chieti, Italy), Laetitia Martinerie (Paris, France) and Franco Chiarelli (Chieti, Italy; Consultant).

Comments and contributions are very welcome. Please contact us at info@espe-elearning.org.

Stenvert LS Drop, Co-ordinator, ESPE e-Learning Programme
Conny de Vugt, Content Manager
Sander Spaans, Webmaster

Research Update: Paediatric and Adolescent Gynaecology continued from page 1

puberty (CPP); subsequently, *MKRN3* mutations were also reported in isolated cases of CPP. In this population-based, longitudinal study in Danish girls, Hagen *et al.* report that decreasing levels of *MKRN3* precede pubertal onset in girls, while undetectable or low *MKRN3* levels are observed in patients with early onset of puberty.

Developmental variations in environmental influences including endocrine disruptors on pubertal timing and neuroendocrine control

Parent *et al.* 2015 *Frontiers in Neuroendocrinology* Jan 12. pii: S0091-3022(14)00112-5. doi: 10.1016/j.yfrne.2014.12.004 [Epub ahead of print]

The influence of environmental factors – such as nutrition, stress and endocrine disruptors – on variations in pubertal timing is reviewed using the rodent as a model. The capacity of such environmental factors to modify the functioning of the neuroendocrine system seems to be maximal during prenatal and early postnatal life, becoming less relevant as puberty approaches.

Endocrine disorders in adolescent and young female athletes: impact on growth, menstrual cycles and bone mass acquisition

Maimoun *et al.* 2014 *Journal of Clinical Endocrinology & Metabolism* 99 4037–4050

The effects of overtraining and/or poor dietary intake on endocrine function in girls are reviewed, specifically regarding growth, menstrual cycles and bone mass acquisition. Recent findings highlight the endocrine role of adipose tissue and energy balance in the regulation of homeostasis and reproductive function. A better understanding of the mechanisms whereby intense training affects the endocrine system may orient research towards developing innovative strategies to improve the medical care of these adolescents and protect their reproductive function.

New clinical guidelines in PAG

The Pediatric Endocrine Society invited an expert group of representatives from the Androgen Excess–PCOS Society, as well as stakeholder international paediatric and adolescent specialty societies, to define the criteria which have sufficient evidence to support their use in the

diagnosis of PCOS in adolescents. The results have been published as Witchel *et al.* 2015 The diagnosis of polycystic ovary syndrome during adolescence *Hormone Research in Paediatrics* PMID: 25833060 [Epub ahead of print].

In addition, ESPE is considering organising a consensus meeting on the diagnosis and treatment of PCOS in adolescence, to fill in the gaps that remain.

Forthcoming activities of the PAG Working Group

In 2015, our symposium will focus on the short and long term challenges for the reproductive system after malignancies, with special emphasis on the preservation and restoration of fertility, and on the diagnosis and management of gynaecological conditions.

We also intend to initiate a collaborative clinical project on the prevalence of hyperandrogenism in adolescent girls previously treated for central precocious puberty and followed up for at least 2 years after menarche.

Lourdes Ibáñez, Co-ordinator
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ESPE 2015: speakers' previews

We are delighted to bring you details of the talks by some of the invited speakers at the forthcoming 54th Annual Meeting of ESPE in Barcelona, Spain, on 1–3 October. To see the programme, visit www.espe2015.org/programme.aspx.

Register by 8 June to take advantage of the early bird rate. See www.espe2015.org/registration.aspx.



Molecular mechanisms of growth plate adaptation during under-nutrition

ALMOST 180 MILLION CHILDREN IN THE WORLD have stunted growth. Most live in eastern and central Africa and in south-central Asia. Among multiple factors causing stunted growth in the developing world, malnutrition is the most important. Reduced caloric intake is also a cause of poor statural growth in developed countries.

Mammals (including humans) exposed to malnutrition experience poor bone growth through adaptive mechanisms affecting endocrine factors, as well as paracrine factors, in the growth plate. For instance, malnutrition-related deficiencies of endocrine factors such as insulin-like growth factor (IGF)-1, insulin and leptin lead to impaired statural growth. It has also been shown that microRNAs and enzymes like

sirtuin1 may be implicated in growth adaptation during malnutrition by regulating the activity of systemic and paracrine growth factors.

Lastly, recent evidence indicates that the changes in expression of fibroblast growth factor-21 (FGF-21) associated with caloric reduction can adversely affect growth plate chondrogenesis and bone growth both systemically and locally within the growth plate. Increased FGF-21 action during chronic under-nutrition causes growth hormone resistance/IGF-1 deficiency and, in turn, reduced growth plate function and bone growth.

Francesco De Luca, Philadelphia, PA, USA

(Learn more by attending talk S10.1 on 3 October at 15.30)

Transgenerational developmental programming of endocrine disease

OVER 20 YEARS AGO, EPIDEMIOLOGICAL STUDIES revealed an association between early growth and long term risk of metabolic diseases, including type 2 diabetes. This led to the hypothesis of the developmental origins of health and disease – the concept that the environment experienced during critical periods of development, such as *in utero* nutrition, has a permanent impact on long term health.

The initial focus was directed towards the detrimental effects of low birth weight and early under-nutrition. However, in light of the obesity epidemic, more focus is now being directed towards the detrimental effects of early over-nutrition. Both fetal under-nutrition and over-nutrition have the same phenotypic consequences in terms of metabolic disease risk. However, it remains to be established if they mediate their effects through the same mechanistic pathways.

Animal models have been invaluable in identifying mechanisms underlying developmental programming. Many rodent models have

been established to mimic the human situation and allow studies across the life course. From such studies three key programming mechanisms have emerged: (i) permanent structural changes, i.e. the idea that if, during a critical period of development, an organ is exposed to a suboptimal level of a key hormone or nutrient required for its development, this will have a permanent impact on organ structure and function; (ii) accelerated cellular ageing as a consequence of oxidative stress; (iii) epigenetic programming of gene expression through changes in DNA methylation, histone modifications and microRNAs. Further understanding of these mechanisms may give us the potential to ultimately develop markers of disease risk and help to design rational intervention strategies.

Susan E Ozanne, Cambridge, UK

(Learn more by attending talk S5.2 on 2 October at 15.00)

Is brown adipose tissue relevant to paediatrics?

THIS TALK WILL HIGHLIGHT PROGRESS in paediatric brown adipose tissue (BAT) research over the past decade, including the general acceptance that this tissue is much more prevalent in children than in adults, and in infants than in children.

Available longitudinal data in paediatric patients provide strong evidence to support an inverse association between BAT activity and white adipose tissue (WAT) accumulation, most strikingly in the intra-abdominal depot. Moreover, a positive association between muscle volume and the amount of BAT has been reported in both boys and girls. Adolescents and post-pubertal teenagers that depict BAT on positron emission tomography examinations have significantly greater muscle volume than those without identifiable BAT.

Infancy is a developmental stage associated with concurrent gains in skeletal muscle and large amounts of BAT, but low levels of physical

activity. During the first 3 months of life, infants experience striking musculoskeletal development, despite being relatively motionless and spending most of the day asleep. Interestingly, we found that the amount of BAT decreases concomitantly with increases in muscle during infancy, consistent with the notion of a feedback loop between BAT and muscle.

Although the lack of techniques to measure BAT has limited our understanding of its relevance to human physiology, advances in magnetic resonance imaging techniques based on the cytological differences in lipid content and the degree of vascularisation between BAT and WAT allow for the quantification of BAT, even in healthy infants.

Vicente Gilsanz, Los Angeles, CA, USA

(Learn more by attending talk S2.2 on 1 October at 14.30)

ESPE award winners 2014



In issue 26 of the ESPE Newsletter (Winter 2014, pages 3–4), we reported the award winners from the 53rd Annual Meeting of ESPE in Dublin last September. Now we are delighted to talk to some of them in person, and to find out what their prize has meant to them and to their research.

Andrea Prader Prize winner:

Jean-Pierre Bourguignon

THIS PRIZE WAS VERY DIFFERENT, because my peers had nominated me for a lifetime achievement. I felt it was like a gift from the network of people who have accompanied short or long parts of my journey in paediatric endocrinology. Such a trip is always a long story, with both exciting and disappointing episodes, where the overall direction of the

work appears as important or even more important than the pieces of work themselves.

The day before I received the prize, I was quite anxious about whether my lecture would be interesting. I came across a colleague who knew I was the recipient. He rightly stressed that there were as

'The role of those of us who are Andrea Prader Prize recipients is to shed new light from our past onto the future of others.'

many different profiles of Andrea Prader Prize lecturers as there were recipients and concluded, 'Just be yourself!'

How does this prize push the boundaries of paediatric endocrinology?

My co-workers and I twice received the Henning Andersen Prize, which we felt gave a real boost to our research. The Andrea Prader Prize comes at a time in life when you are thinking about the entire landscape more than about your own tree and its fruits (though, as a colleague of mine pointed out, old trees do not bear old fruits!). The role of those of us who are Andrea Prader Prize recipients is to shed new light from our past onto the future of others. However, I do not feel in a position to give lessons to anyone, and rather want to share the lessons I have learnt myself, while leaving it to others, particularly younger colleagues, to consider those while building their future. This message, which I attempted to give in my prize lecture, is that 'questioning does not stop with finding'.

Where has your clinical and research work taken you?

Under the direction of my late mentor Paul Franchimont, I became interested in the mechanism of puberty as long ago as 1972, before graduating as an MD. It took me decades to become aware that, because puberty is crucial for species' survival, redundancy is protectively characterising the mechanism. So, investigators will be



kept busy for a few more decades (as I was) before they eventually come to the ultimate key in that neuroendocrine mechanism.

A colleague of mine described me as a 'monomaniac' for my approach to research. This may have been the case, but is no longer, since we have embarked on studies of endocrine-disrupting chemicals (EDCs) and extended our interest from the hypothalamus to other brain areas. As a paediatric endocrinologist, I am fascinated by the concept of the developmental origin of health and disease, which has huge implications for EDC research and also for patient education, particularly in informing pregnant women and parents of young children about the precautionary principle.

Where is paediatric endocrinology heading in the next 5-10 years?

For the past 3 years, I have started to interact with stakeholders and policymakers in order to value the contribution of (paediatric) endocrinology in the EDC arena. This has been an opportunity to become aware of some gaps between health sciences and the rest of the society. Beyond our efforts to promote training of young colleagues, paediatric endocrinologists have a mission to educate those setting the financial resources for research and the regulations for society. This is particularly challenging in a context of increasing and unequally disclosed conflicts of interest or biases. Again, the first step is self-questioning before calling others into question. Then follow Albert Einstein's suggestion: 'Learn from yesterday, live for today, hope for tomorrow. The important thing is to not stop questioning.'

Jean-Pierre Bourguignon, Liège, Belgium

ESPE Research Award winner:

Moshe Phillip

WE ARE BASED AT the Jesse Z and Sara Lea Shaffer Institute for Endocrinology and Diabetes, at Schneider Children's Medical Center of Israel. As part of the ongoing fight to help children with endocrine problems including diabetes, the Institute invests much effort in both basic and clinical research.

The underlying aspects of the molecular basis of endocrine diseases are studied in the Pediatric Endocrinology and Diabetes Research Laboratory adjacent to the hospital. The proximity of the laboratory to the clinical service, and the close teamwork between laboratory researchers and medical care providers, enable us to transfer the patient's problem directly from the clinic to the laboratory, where innovative solutions are sought and vice versa.

The clinical research unit comprises clinicians, nurses, dieticians, psychologist and social workers, as well as several clinical research co-ordinators. A vast variety of clinical research projects are under investigation at any given time including intervention studies in endocrine diseases and diabetes.

Recently, we have been engaged in research in two main areas:

- investigating the relationship between nutrition and growth
- improving the metabolic control and quality of life of patients with diabetes.

Nutrition and growth

Our studies aim to find the factors that influence bone growth and are focused on changes within the growth plate. One of the outcomes is the use of knowledge we have gained to develop an enriched diet to be consumed by children in the evening before bedtime. This formula was studied in a double blind, randomised, placebo-controlled study with 200 subjects and, as a result, it is now being commercially produced and will be distributed internationally. It will be given to normal short and lean children who have no indication for medical treatment such as growth hormone.



Artificial pancreas

Extensive research shows that tight glucose control is the primary factor in avoiding the devastating complications of diabetes. However, this is associated with an increased risk of a severe hypoglycaemic episode, which is one of the most feared and dangerous events for patients and their parents. So the ultimate challenge is to keep blood glucose within a normal range without severe hypoglycaemic events. Although new advanced technologies have recently been introduced, patients' diabetes control and quality of life have not yet dramatically improved.

With this in mind, we established the Diabetes Technology Center (DTC), focusing solely on new technologies in diabetes, and, in particular, towards achieving an artificial pancreas system. The staff of the DTC have developed the MD-Logic system, which links sensors with insulin pumps via novel computerised control algorithms that dictate insulin delivery in response to real-time glucose sensor data. The MD-Logic system was tested in a number of studies, assessing its safety and efficacy. Our system was the first to be tested outside the hospital at a diabetes camp, but the greatest breakthrough was testing our system at a patient's home during a regular daily routine.

Our artificial pancreas technology has recently received the CE mark and was licensed for integration into insulin pumps made by Medtronic.

Moshe Phillip, Petah Tikva, Israel

ESPE Young Investigator Award winner:

Oliver Semler

I FELT VERY GRATEFUL TO MY TEAM, which was honoured by the award I received. It was a compliment to our clinical work in taking care of patients with osteogenesis imperfecta in an interdisciplinary team.

Our work includes genetic and basic science research to understand new molecular findings regarding causes of brittle bones, as well as clinical trials investigating new physiotherapy or pharmacological treatments. Based on the genetic results, we have been able to initiate a new approach to treatment with an antibody against osteoclasts. This might offer a future alternative to the current bisphosphonate treatment of children with osteogenesis imperfecta.

Our next steps will be to describe the pathophysiological steps causing brittle bones in more detail, working together with international partners to improve the treatment, independence and quality of life of these patients. The cycle of translational research will always continue by characterising patients, investigating the differences between them and adapting therapies based on these new insights.

Oliver Semler, Köln, Germany



IN MEMORIAM

Hans Helge

1935-2015

IN FEBRUARY 2015, HANS HELGE, former Chairman of Paediatrics and Paediatric Endocrinology at the Free University of Berlin, Germany, peacefully passed away surrounded by his family. The paediatric endocrine community is immensely saddened by this loss of a pioneer of paediatric endocrinology both in Germany and across Europe.

Hans Helge was one of the first students and a graduate of the Free University of Berlin, which was founded in 1948 following the division of the city. He received his MD and PhD there in 1956. After his medical internship he worked as a research fellow in the Department of Pathology in Kiel and again in Berlin from 1956 to 1958.

In 1958 he began his medical training in paediatrics at the Free University's children's hospital. Subsequently, he undertook paediatric fellowships at the Johns Hopkins University in Baltimore (MD, USA) – the birthplace of paediatric endocrinology – and at the University of Miami (FL, USA), where he worked with Bill Nyhan on rare inherited disorders of metabolism.

After returning to Berlin, he completed his thesis for a professorship on the intracellular distribution of cyclophosphamide in tumour cells. In 1968, he moved to the children's hospital at the University of Heidelberg under the directorate of Horst Bickel, a pioneer in paediatric metabolic diseases and founder of



newborn screening for phenylketonuria in Germany. Here, Hans worked as Assistant Professor in Paediatric Endocrinology. fields worked together to improve patient health. His leadership resulted in a growing number of paediatric subspecialties, clinics and institutes with academic chairs, and so the department developed into a nationally and internationally renowned paediatric institution.

Throughout his professional life as a physician–scientist, paediatrician and paediatric endocrinologist, he was eagerly engaged in fostering a new generation of paediatric endocrinologists. He infected everybody with his insatiable curiosity and enabled achievements which his mentees would never have thought possible. He was a true teacher, who never exploited his students and colleagues to benefit his own career and always stimulated international exchange.

In 1982/1983, already well established as Paediatric Chairman, Hans followed his scientific impulses and spent a sabbatical at Baylor College in Houston (TX, USA), where he learned innovative methods for the non-invasive study of metabolism using stable isotopes.

One major achievement was the introduction of a population-based programme to screen all newborns in Berlin for congenital hypothyroidism, as long ago as 1978. The general population-based programmes in Germany only followed in 1981. His pioneering and respected

studies on the impact of dioxin and PCBs (polychlorinated biphenyls) in breast milk using stable isotopes, and also on the effects of anti-epileptic drug use during pregnancy on child development, might be unknown to his colleagues in endocrinology, but reflect his broad scientific interest and capabilities.

In paediatric endocrinology, Hans was a pioneer of growth hormone measurement and diagnostics. He contributed to our understanding of thyroid physiology in early infancy, enabled the treatment of precocious puberty with cyproterone acetate and encouraged molecular genetic studies in paediatric endocrine disorders. Thus, he provided important contributions to modern paediatric endocrinology, and was often at the forefront of cutting-edge topics like pituitary disease, thyroid hormone metabolism and brain development and paediatric pharmacology.

Hans Helge was an active member and chairman of many committees in the German Endocrine Society, being President and Vice-President, and very involved in the German Society for Paediatrics. But ESPE was his real scientific family. He attended almost every annual meeting since ESPE's foundation, the last time being in Milan in 2013. Here, he and his wife Inge would meet friends from all over the world. They developed many personal relationships with colleagues from Europe and the USA, reflecting Hans' kindness and loyalty.

After his retirement, Hans and Inge enjoyed life with their family of four children and growing number of grandchildren. And it was wonderful that his love and care for children could now be experienced by his own family, who must have missed out when Hans had been so busy with his work for long hours, weekends and holidays.

The paediatric and paediatric endocrine world will miss Hans not only as a pioneer, physician–scientist and mentor, but also for his humanity and as a critical and inspirational role model.

Annette Grüters-Kieslich

Director, Department of Paediatrics, and Chair, Paediatric Endocrinology and Diabetology, Charité Universitätsmedizin Berlin, Germany

'He infected everybody with his insatiable curiosity and enabled achievements which his mentees would never have thought possible.'

In 1972 he came 'home' to Berlin and was appointed as full Professor and Chairman of Paediatrics at Kaiserin Auguste Victoria Haus, still the children's hospital of the Free University of Berlin. He put enormous energy into the development of a Department of Paediatrics, following his experiences in the USA, where specialists and experts from all

Yearbook of Pediatric Endocrinology: Editor's preview

Editor Ken Ong picks out an outstanding paper included in the forthcoming Yearbook of Pediatric Endocrinology.

Hormone changes in peripubertal girls

Biro FM, Pinney SM, Huang B, Baker ER, Walt Chandler D & Dorn LD *Journal of Clinical Endocrinology & Metabolism* 2014 **99** 3829–3835

BACKGROUND: Studies of circulating hormone concentrations in the peripubertal period report a temporal rise in adrenal hormones prior to the rise in sex steroid levels. The authors aimed to examine the relationships between changes in adrenal and sex hormones in 252 peripubertal girls.

METHODS: A longitudinal observational study was conducted between 2004 and 2010 in school districts at the Cincinnati site of the Breast Cancer and Environment Research Centers. Girls aged 6–7 years old were recruited and assessed by female investigators every 6 months for height, weight and puberty status. At each visit, a fasting blood sample was collected and analysed for concentrations of androstenedione, oestradiol, oestrone and testosterone by high-performance liquid chromatography (HPLC) with tandem mass spectrometry at Esoterix Laboratories (California, USA), and also for dehydroepiandrosterone-sulphate (DHEA-S) and sex hormone-binding

globulin (SHBG). Changes in these concentrations were tested from 30 months prior to breast development until 6 months afterwards.

RESULTS: A rise in DHEA-S concentrations was detectable between 30 and 18 months before breast development. Androstenedione and oestrone increased 12–18 months before breast development.

Increases in oestradiol and testosterone, and reductions in SHBG, were detectable 6–12 months before breast development. Girls with a higher body mass index (BMI) had lower oestradiol concentrations at the start of breast development and also 6 months afterwards.

CONCLUSIONS: Sequential rises in serum DHEA-S, then oestrone, then oestradiol concentrations precede breast development. The lower oestradiol levels observed in heavier peri-pubertal girls suggests breast development due to peripheral conversion of adrenal androgens to oestrone.

COMMENTARY

These findings reveal interesting insights into the onset of puberty in girls. The authors used a novel hormone assay in a carefully designed study of girls with frequent clinical and biochemical evaluations during the pre- and peripubertal years. They propose the following messages.

First, the findings support Ducharme's original suggestion that adrenal steroids trigger the re-initiation of the hypothalamic-pituitary-gonadal (HPG) axis.¹ This is inferred by remembering that, while testosterone is aromatised to oestradiol, androstenedione is converted to oestrone (which accordingly is the most common oestrogen in post-menopausal women). Pubertal onset, at least as indicated by breast development, followed about 2 years after the first detection of a rise in peripheral DHEA-S, followed first by a rise in oestrone, and only 6 months later by a rise in oestradiol and a fall in SHBG.

Secondly, in contrast to this 'pubertal thelarche' pathway, girls with a higher BMI reach thelarche with apparently less HPG axis activation. This is indicated by lower oestradiol levels, and the implied mechanism

is greater local aromatisation of adrenal androgens at the target tissues. The authors suggest that this may explain why secular changes towards younger age at thelarche have been observed without similar secular changes in oestradiol concentrations and with weaker trends in age at menarche.²

The gradual rises in oestrone and oestradiol concentrations starting 12–18 months before breast development challenge our clinical paradigm of an abrupt onset of puberty coincident with the start of pulsatile gonadotrophin-releasing hormone secretion by the hypothalamus. Future clinical validation and use of such ultra-sensitive hormone assays may lead to greater appreciation of a continuum in pubertal onset, and allow us to better understand the environmental factors that are promoting pubertal development at increasingly younger ages.

1. Ducharme JR *et al.* 1976 *Journal of Clinical Endocrinology & Metabolism* **42** 468–476.
2. Aksela L *et al.* 2009 *Pediatrics* **123** e932–e939.

Dutch Society for Paediatrics - Endocrinology Section

DUTCH PAEDIATRIC ENDOCRINOLOGISTS collaborate through the Endocrinology Section of the Dutch Society for Paediatrics (Nederlandse Vereniging voor Kindergeneeskunde; NVK-ES), founded in 1892. Currently it has around 175 members, led by their President Euphemia C A M Houdijk.

The NVK-ES has several working groups, which aim to share professional interests and to promote collaborative research and training, in order to improve the quality of care of Dutch paediatric endocrine patients. The groups and their co-ordinators are:

- congenital adrenal hyperplasia (Hedi.Claahsen@radboudumc.nl)
- congenital hypothyroidism (A.S.vanTrotsenburg@amc.uva.nl)
- diabetes mellitus (p.stouthart@orbisconcern.nl)
- growth hormone (c.noordam@cukz.umcn.nl)
- obesity (e.g.vanmil@jzb.nl)
- Turner syndrome (e.l.t.vandenakker@erasmusmc.nl)

Reference centres are in place for growth hormone studies on small for gestational age and Prader–Willi syndrome (Erasmus MC, Rotterdam), congenital adrenal hyperplasia (Nijmegen), thyroid (Amsterdam MC), longitudinal growth (Leiden), and anti-FGF23 (anti-fibroblast growth factor 23) in hypophosphataemic rickets (Groningen).

The NVK-ES organises two annual meetings, as well as a yearly Masterclass in Paediatric Endocrinology. Their clinical guidelines are available at www.nvk.nl. The fellowship programme including the learning goals is included in the Masterclass for fellows and paediatric endocrinologists.

For further information, visit www.nvk.nl or contact Annemieke M Boot (a.m.boot@umcg.nl).



Future meetings

See www.eurospe.org/meetings for details of all future meetings



Other Events

ESPE Science School

3-6 June 2015
Lake Annecy, France

ESPE Summer School

28-30 September 2015
Poblet Monastery, Catalonia, Spain

2nd ESPE Caucasus & Central Asia School

29 October-3 November 2015
Tashkent, Uzbekistan

5th ESPE Maghreb School

18-23 November 2015
Tunisia

Deadlines

Please note these fast-approaching deadline dates and submit your applications as soon as possible.

ESPE Clinical Fellowship applications	31 May 2015
ESPE 2015 Early Bird Registration deadline	8 Jun 2015
ESPE Visiting Scholarship applications	31 Jul 2015
ESPE 2015 Standard Registration deadline	3 Aug 2015
ESPE Winter School applications (opening shortly)	23 Oct 2015
ESPE Visiting Scholarship applications	31 Oct 2015
ESPE Andrea Prader Award nominations	10 Dec 2015
ESPE Research Award nominations	10 Dec 2015
ESPE Young Investigator Award nominations	10 Dec 2015
ESPE Outstanding Clinician Award nominations	10 Dec 2015
ESPE International Award nominations	10 Dec 2015
ESPE Henning Anderson Award nominations	10 Dec 2015

See the ESPE website at www.eurospe.org for further details and the application process



European Society for Paediatric Endocrinology

Improving care of children with endocrine diseases by promoting knowledge and research

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ESPE Office

The ESPE Office is managed by Bioscientifica Ltd. The role of ESPE's Senior Operating Officer is undertaken by Joanne Fox-Evans and Lucy Lawrance. They oversee the day-to-day activities of ESPE, liaising with the ESPE Council and committee members as well as being the main point of contact for ESPE enquiries. They undertake projects requested by the Secretary General, providing him with assistance and attending ESPE Council and committee meetings. Tracey-Leigh Meadowcroft handles membership renewals and payments and deals with subscriptions to *Hormone Research in Paediatrics*.

Bioscientifica also manages the Corporate Liaison Board which deals with industry sponsors, and is also responsible for publication of the ESPE Newsletter and monthly news alerts.

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